APPENDIX 2

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Prospective observational cohort safety study to monitor the introduction of a non-CFC formulation of salbutamol with HFA134a in England

P.M. Craig-McFeely[1,2], L.V. Wilton[1], J.B. Soriano[3,4], W.C. Maier[3] and S. A.W. Shakir[1]

[1]Drug Safety Research Unit, Southampton, [2]Hillbrow Surgery, Liss, [3]GlaxoSmithKline, Greenford, and [4]London School of Hygiene and Tropical Medicine, London, UK

Key words
salbutamol MDI-CFC-free (HFA propellant) – asthma in primary care – pharmacovigilance

Abstract. Objective: To monitor the safety of a salbutamol MDI with a hydrofluoroalkane propellant (Ventolin Evohaler) during its introduction into primary care use in England. Methods: Prospective observational cohort study. 1,365 GPs in England submitted data on 10,472 regular users of Ventolin MDI, over five 3-month periods of observation between October 1, 1998 and December 31, 1999. The primary aim was to compare event rates occurring before and after the introduction of Ventolin Evohaler. The secondary aim was a comparison of event rates between users of Ventolin Evohaler and Ventolin MDI. The main outcome measures were: indication for use of Ventolin MDI, assessment of disease severity, event rates during each period of observation; deaths, pregnancies, reported adverse drug reactions and reasons for discontinuation of MDI. Event rates were adjusted using a ratio for under-reporting derived from a validation study on 4.6% of the study population and stratified by severity of indication. Results: The primary indication was asthma in 94%, distributed by severity as 47% mild, 44% moderate and 9% severe; 13% were children. By October 1999, 52.7% of the 8,973 remaining patients had transitioned to Ventolin Evohaler. There was no increase in major or minor events observed following the introduction of Ventolin Evohaler. No serious adverse events, abnormal pregnancy outcomes or deaths have been related to Ventolin MDI or Ventolin Evohaler. The validation study showed a degree of under-reporting. Conclusion: These results on a large cohort of community patients in England indicate that Ventolin Evohaler is well tolerated among asthmatics.

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Correspondence to
Dr. P. Craig-McFeely
Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton SO31 1AA, UK
patrickcmf@doctors.org.uk

Introduction

To eliminate the environmental damage caused by chlorofluorocarbon (CFC), the Montreal protocol recommended the phasing out of CFC propellants in metered dose inhalers (MDIs) [Montreal Protocol 1987]. MDIs are safe, effective drug delivery systems used to treat respiratory disease [British Thoracic Society et al. 1997]. A salbutamol MDI using a non-CFC propellant, hydrofluoroalkane (HFA)134a (Ventolin Evohaler, GlaxoSmithKline), was introduced in England on January 18, 1999. Thereafter, supplies of the CFC-containing MDI (Ventolin MDI) were withdrawn and several hundred thousand users transitioned to an alternative inhaler.

The development of Ventolin Evohaler required significant pharmaceutical and technical changes to the inhalation device as well as a change of salbutamol, the active substance, from free base to salbutamol sulfate. Controlled trials showed no differences in terms of efficacy or safety between salbutamol MDIs using a CFC or HFA134a propellant [Baumgarten et al. 2000, Lumry et al. 2001, Shapiro et al. 2000]. A postmarketing safety study of the first salbutamol MDI with HFA134a propellant (Airomir, 3M) showed no differences between the CFC and HFA inhalers in 6,614 patients observed for 3 months, in terms of hospital admissions or total adverse events although significantly more patients using the HFA inhaler withdrew from the study [Ayres et al. 1998]. We studied a much larger population (10,492 enrolled and 8,973 completing 12 months of observation) to monitor the safety of the transition by conducting a prospective observational cohort study of regular users of Ventolin MDI. The primary aim was to compare the event rates occurring before and after the introduction of Ventolin Evo-

haler in all patients irrespective of final inhaler. The secondary aim was a comparison of event rates between users of Ventolin Evohaler and Ventolin MDI.

Methods

Ethical approval

This study was done in accordance with guidelines in respect of studies utilizing anonymized data extracted from patient records [CIOMS/WHO 1993, Medicines Control Agency et al. 1994]. Ethical committee approval and written patient consent were obtained for all patients in the validation study.

Study design

General practitioners (GPs) recruited over 10,000 regular and current users of Ventolin MDI in England identified from the prescribing record prior to the launch of Ventolin Evohaler. Use was defined as 2 or more prescriptions in the previous year. All GPs throughout England were invited to recruit with no restriction placed on the severity of the indication but they were asked to preferentially recruit those patients with asthma. Patients were followed using event data extracted by GPs from the medical records for 12 months from the launch of Ventolin Evohaler. Quarterly interim reports were sent to the Medicines Control Agency (MCA). Patient management followed normal clinical practice with no additional requirements or visits to the doctor. There was no influence on the GP's prescribing decision once Ventolin MDI became unavailable. Recruitment reflected the prescribing habits for Ventolin MDI in general practice for the management of asthma.

Data collection

There were five 3-month periods of observation. The first period (baseline) was between October 1 and December 31, 1998, prior to the launch of Ventolin Evohaler. The study ended on December 31, 1999. In January 1999, GPs were sent 2 questionnaires, 1 requesting baseline patient characteristics and disease severity and the first follow-up questionnaire to cover the baseline period requesting information on inhaler exposure and patient events. Similar follow-up questionnaires, with reminders to non-responders, were sent every 3 months until January 2000. The baseline questionnaire had 7 questions with tick boxes for answers (Yes, No, Don't know) and free text for some questions: the number of years since starting a Ventolin Inhaler; the indication (asthma or free text for alternative); severity (mild, moderate or severe); hospitalization for the indication in the past year and number of admissions; need for other regular treatment with details in free text, if applicable; need for intermittent courses of oral steroids and whether patient smoked. The follow-up questionnaires had 6 questions with tick boxes for answers and free text for event information; has patient used Ventolin Evohaler since (date of end of previous 3-month period supplied), if yes, date Ventolin Evohaler dispensed and is a spacer used regularly; has Ventolin Evohaler been stopped, if yes, date stopped or date last prescription; use of other metered dose inhaler in preceding 3 months, if yes, details in free text; need for intermittent courses of oral steroids, if yes, how many courses, is patient current smoker; any events in preceding 3 months, if yes, date of each event with details in free text. There was additional follow-up of pregnancies, deaths and events of special interest.

Validation

A validation study, to estimate accuracy of reporting and the effect of confounding variables, was conducted on a random sample of 412 patients (4.6% of study population). The information entered by the GP on to the study form was compared with information extracted from the practice medical records by a research assistant. The validation study indicated that more events were recorded in the medical notes than had been reported on the study follow-up questionnaires and that under-reporting including under-reporting of serious adverse events has occurred. It also showed that the reporting of events improved with time. The event rates were adjusted by the proportion of under-reporting found in

Table 1. Summary of baseline characteristics at enrolment and at completion for all patients.

	Period	
	Oct – Dec 1998	Oct – Dec 1999
Surveyed (n)	13,698	8,221
Returned (n)	11,668	8,194
Response rate (%)	84.4	99.7
Void (n)	1,096	221
Sample size (n)	10,472	8,973
Mean age (SD)	41.1 (22.6)	41.0 (22.5)
Children aged 12 and under (%)	12.8	12.8
Sex (% female)	50.1	50.2
Duration of prior Ventolin use (%)		
< 1 year	5.4	5.2
1 – 10 years	53.7	53.7
> 10 years	40.5	40.7
Not specified	0.4	0.4
Indication for Ventolin (total to 100%)		
Asthma (%)	93.6	94.0
COPD (%)	4.0	3.8
Other (%)	2.4	2.2
Asthma severity (%)		
Mild	46.7	47.5
Moderate	43.8	43.3
Severe	9.2	8.6
Not specified	0.3	0.3
Smoker (%)	18.0	17.5
Intermittent oral steroid use (%)	28.4	26.6
Asthma hospitalization in past year (%)	4.3	3.9
Other regular asthma treatment		
Inhaled steroids (%)	69.0	68.7
Long-acting β-agonists (%)	11.8	11.6
Theophylline (%)	4.7	4.6
Anticholinergics (%)	6.0	5.8
Cromones, e.g. cromoglycate (%)	1.2	1.3
Short course of oral steroids in past 3 months (%)	11.3	8.9[1]
Ventolin inhaler stopped (%)	1.2	2.7
Ventolin Evohaler stopped (%)	—	0.8
Ventolin Evohaler exposure (%)	—	52.7

[1] = significantly less common ($p < 0.05$) during the fifth period of observation compared to the first.

each 3-month period for individual events. In addition, the validation study found that 20.5% of the cohort had had only 1 Ventolin MDI prescription or a salbutamol MDI in 1998 and 5.4% had no record of any form of salbutamol MDI in 1998 (i.e. had failed to satisfy the eligibility criteria of 2 or more prescriptions for Ventolin MDI in the year preceding enrolment).

Event definition

An event was defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected MDI related reaction, any alteration of clinical importance in laboratory values or any other complaint which was con-

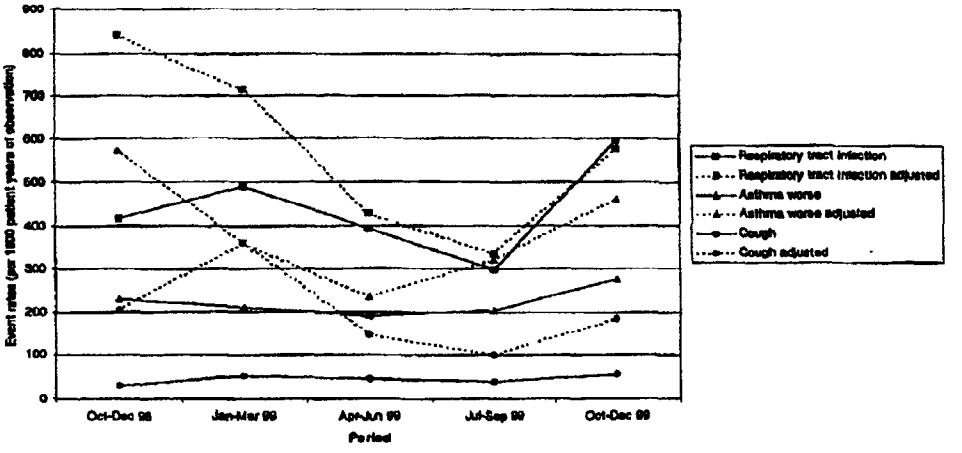

Figure 1a. Crude rates and rates adjusted by proportion of under-reporting for each of the common respiratory events by study period.

Supporting table to Figures 1a and 1b. Event numbers from validation study for events significantly more common in fifth period of observation compared to the first in the whole study.

	Event numbers from validation study (412 patients) Period									
	Oct – Dec 1998		Jan – Mar 1999		Apr – Jun 1999		Jul – Sep 1999		Oct – Dec 1999	
GP/Validation (Val) reported event numbers	GP	Val	GP	Val	GP	Val	GP	Val	GP	Val
Event										
Respiratory tract infection	56	113	69	101	59	64	16	18	35	34
Asthma worse	24	59	20	34	22	27	7	11	15	25
Depression	1	9	6	12	6	12	3	4	2	2
Cough	7	46	5	34	6	19	4	10	4	13
Pain joint	3	12	4	13	2	11	5	3	1	3
Infection skin, unspecified/local bacterial	3	7	4	6	10	13	2	4	2	3
Headache, migraine	2	8	1	11	1	7	2	2	1	2

sidered of sufficient importance to enter in the patient's notes [Mann 1998].

Statistical methods

A sample size of 8,806 patients would detect a 3-fold increase and a sample size of 4,995 would detect a 4-fold increase in event rates of a specific event occurring at a frequency of 1 per 1,000 or higher at baseline, with 95% confidence and 80% power, for 2 or more time points.

Rates for all events were calculated for each period. For events, rates where the 95% confidence intervals for 2 periods did not overlap an incidence density rate ratio (IRR) was calculated. The unadjusted IRR used a Poisson rate model including time on MDI within that period until onset of the event as the exposure. This analysis was carried out using the statistical software STATA (Release 6.0. Stata Corporation, Texas, 1999).

Event rates in the primary analysis were adjusted for estimated under-reporting by multiplying by the ratio between the number

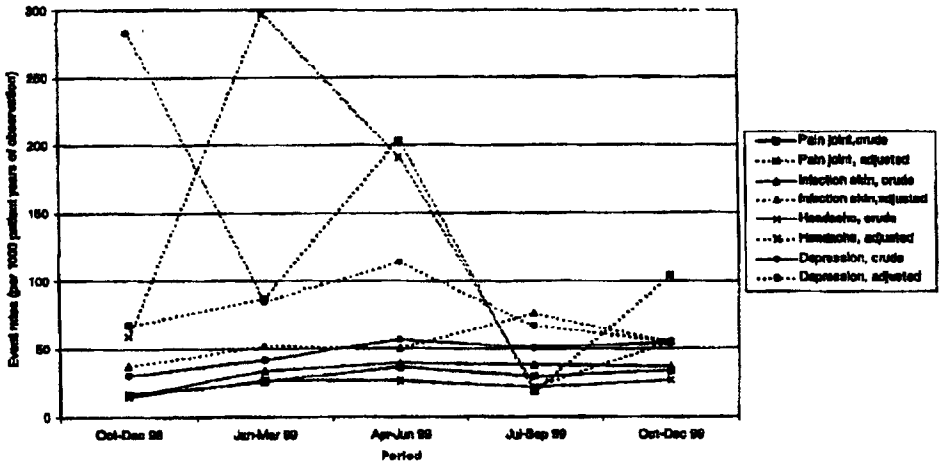

Figure 1b. Crude rates and rates adjusted by proportion of under-reporting for each of the common non-respiratory events by study period.

Supporting table to Figures 1a and 1b. Event incidence densities (with 95% confidence intervals) by period for all patients (ordered by density during first period of observation) for events significantly more common in fifth period of observation compared to the first.

	Event rates (per 1,000 patient years of observation) by Period				
	Oct – Dec 1998	Jan – Mar 1999	Apr – Jun 1999	Jul – Sep 1999	Oct – Dec 1999
Patient years of observation	2,640	2,440	2,378	2,325	2,262
Event					
Respiratory tract infection	417.0* (392.6 – 442.0)	489.3 (462.0 – 517.5)	393.2 (368.4 – 418.8)	299.4 (277.5 – 322.0)	592.0* (560.7 – 624.1)
Asthma worse	232.2* (214.2 – 250.9)	211.5 (193.6 – 230.1)	192.2 (175.0 – 210.2)	204.3 (186.3 – 223.1)	276.7* (255.5 – 298.8)
Depression	31.4* (25.0 – 39.0)	42.6 (34.8 – 51.2)	57.2 (48.0 – 67.2)	51.2 (42.4 – 60.8)	55.7* (46.4 – 65.9)
Cough	31.4* (25.0 – 39.0)	53.3 (44.5 – 62.8)	46.3 (38.0 – 55.3)	40.4 (32.7 – 49.5)	56.6* (47.2 – 66.8)
Pain joint	17.0* (12.4 – 22.8)	26.6 (20.6 – 34.0)	37.0 (29.7 – 45.6)	30.1 (23.5 – 38.0)	34.5* (27.3 – 43.0)
Infection skin, unspecified/local bacterial	16.3* (11.8 – 21.9)	34.4 (27.5 – 42.6)	39.5 (31.9 – 48.4)	38.7 (31.1 – 47.6)	36.7* (29.2 – 45.5)
Headache, migraine	14.8* (10.5 – 20.2)	27.0 (20.9 – 34.4)	27.3 (21.1 – 34.8)	22.4 (16.7 – 29.3)	27.4* (21.0 – 35.1)

* = event rate significantly more common ($p < 0.05$) during the fifth period of observation compared to the first.

of events extracted from the medical records and those reported on questionnaires for each period.

The same methods were used for the secondary analysis, during the fifth period when exposure to Ventolin MDI and Ventolin Evohaler were approximately equal. For selected common events stratification by severity of indication was also carried out.

Supporting table to Figures 1a and 1b. Adjusted event incidence densities (with 95% confidence intervals for periods 1 and 5) by period for all patients for crude event rates significantly more common in fifth period of observation compared to the first.

	Event rates (per 1,000 patient years of observation) Period				
	Oct – Dec 1998	Jan – Mar 1999	Apr – Jun 1999	Jul – Sep 1999	Oct – Dec 1999
Patient years of observation	2,640	2,440	2,378	2,325	2,262
Event					
Respiratory tract infection	841 (730 – 953)	716	427	337	575 (522 – 629)
Asthma worse	571 (488 – 654)	360	236	321	461 (406 – 517)
Depression	283 (207 – 358)	85	114	68	56 (50 – 61)
Cough	206 (158 – 254)	362	147	101	184 (153 – 215)
Pain joint	68 (45 – 98)	87	204	18	104 (75 – 140)
Infection skin, unspecified/local bacterial	38 (33 – 43)	52	51	77	55 (49 – 61)
Headache, migraine	59 (48 – 70)	297	191	22	55 (48 – 62)

Table 2. Incidence density rate ratio (95% confidence intervals) of the 7 events more common in period 5 than in period 1 and the events steroid short course and hospital admission due to asthma worse.

	IRR (95% confidence interval)	
Event	Crude	Adjusted[1]
Pain joint	2.04 (1.37 – 3.05)	2.08 (1.36 – 3.08)
Skin infections	1.81 (1.21 – 2.72)	1.86 (1.23 – 2.80)
Cough	1.84 (1.35 – 2.51)	1.80 (1.32 – 2.46)
Headache/migraine	1.83 (1.15 – 2.89)	1.78 (1.12 – 2.82)
Depression	1.47 (1.07 – 2.01)	1.45 (1.05 – 1.99)
Respiratory tract infections	1.41 (1.28 – 1.55)	1.41 (1.28 – 1.56)
Asthma worse	1.13 (0.99 – 1.29)	1.13 (0.99 – 1.29)
Hospital admission due to asthma worse	0.98 (0.63 – 1.52)	1.06 (0.67 – 1.66)
Steroid short course	0.84 (0.75 – 0.94)	0.85 (0.76 – 0.94)

[1] = controlled for age, sex, time used Ventolin metered dose inhalers, prescribed for asthma, severity, whether hospitalized during previous year, other treatment on a regular basis, intermittent use of oral steroids, smoker. Only cases with complete information on all the controlling variables.

Results

Demographic and baseline data

1,365 GPs supplied anonymized details for 13,698 patients of whom 10,472 were eligible and contributed data at the start of the study and 8,973 (85.7%) supplied data for the entire 15 months of observation. Recruitment was widely distributed throughout England. There were no significant differences in these characteristics as the study progressed (Table 1).

Table 3. Number of events reported by GPs compared to those recorded by research assistant on 412 patients in the validation study used to adjust the rates of the events more common in period 5 than in period 1.

Event	First period			Fifth period		
	GP number of events	Validation number of events	Adjustment ratio[1]	GP number of events	Validation number of events	Adjustment ratio[1]
Respiratory tract infections	66	113	2.0	35	94	0.97
Asthma worse	24	58	2.8	16	25	1.7
Depression	1[2]	6	3.0	2	2	1.0
Cough	7	46	6.6	4	10	3.3
Pain joint	3	12	4.0	1	3	3.0
Skin infections	3	7	2.3	2	3	1.5
Headache/migraine	2	8	4.0	1	2	2.0

[1] = adjusted event rates calculated by multiplying the event rate by this adjustment ratio for each event and period of observation. These adjusted rates are presented graphically in Figures 1a and 1b.

Table 4. Incidence density rate ratio (95% confidence intervals) of common events (for all patients) comparing Ventolin Evohaler cohort to Ventolin MDI cohort during period 5.

Event	IRR (95% confidence interval)	
	Crude	Adjusted[1]
Hospital admission due to asthma worse	1.96 (0.93 – 3.69)	1.64 (0.82 – 3.28)
Asthma worse	1.40 (1.15 – 1.68)	1.29 (1.04 – 1.52)
Steroid short course	1.50 (1.26 – 1.77)	1.24 (1.05 – 1.47)
Headache/migraine	1.21 (0.69 – 2.13)	1.15 (0.65 – 2.04)
Respiratory tract infections	1.19 (1.03 – 1.35)	1.10 (0.97 – 1.26)
Depression	0.68 (0.50 – 1.33)	0.83 (0.55 – 1.26)
Skin infections	0.85 (0.52 – 1.40)	0.93 (0.60 – 1.38)
Cough	0.71 (0.48 – 1.06)	0.68 (0.47 – 1.03)
Pain joint	0.68 (0.42 – 1.08)	0.65 (0.40 – 1.04)

[1] = controlled for age, sex, area, used Ventolin, metered dose inhalers prescribed for asthma, severity, whether hospitalized during previous year, other treatment on a regular basis, intermittent use of oral steroids, smoker. Only cases with complete information on all the controlling variables.

Primary analysis

The events reported most commonly throughout the study were respiratory tract infection and asthma worse. Respiratory-related events had lower rates in the spring and summer relative to autumn and winter. There was no seasonal pattern for non-respiratory related events. Table 2 shows the IRRs of events more common in period 5 compared to period 1 and important events relevant to asthma. Table 3 shows the event rates of 7 common events reported on the questionnaires returned by the GP and from the validation study derived from the medical records. The ratio for each event rate for each period of observation is an estimate of a possible "familiarization" effect. Adjustment of the event rates for under-reporting found in each period reduced the event rate values in

Table 5. Event rates (per 1,000 patient years of observation with 95% confidence intervals) for asthma worse and steroid short course, stratified by severity of indication, for patients on Ventolin MDI or Ventolin Evohaler during the fifth period of observation.

Event	Inhaler	Mild			Moderate			Severe		
		Event rate	95% CI[1]		Event rate	95% CI		Event rate	95% CI[1]	
Asthma worse	Ventolin MDI[2]	141	109 – 178		236[4]	193 – 290		536	471 – 841	
	Ventolin Evohaler[3]	181	144 – 224		371[4]	319 – 427		642	412 – 701	
Steroid short course	Ventolin MDI[2]	91[4]	66 – 122		306[4]	256 – 362		792	606 – 1018	
	Ventolin Evohaler[3]	175[4]	139 – 217		444[4]	387 – 504		776	618 – 962	

[1] = confidence interval, [2] = patient years of observation = 484, [3] = patient years of observation = 484, [4] = significantly higher event rate as 95% confidence intervals for users of Ventolin MDI and Ventolin Evohaler do not overlap.

the later periods and caused the event rate values for respiratory infection, asthma worse, depression, cough and headache/migraine to be lower in period 5 relative to period 1. These results are presented graphically in Figures 1a and 1b.

Secondary analysis

By the study end, exposure to Ventolin Evohaler reported by GPs was 52.7% of the enrolled cohort. The pattern of events was similar in those exposed to either Ventolin inhaler. The incidence density risk ratios for asthma worse and steroid short course were significantly higher for those exposed to Ventolin Evohaler compared to Ventolin MDI (Table 4). Stratification by severity on these crude rates showed these higher rates in patients with mild (for the event steroid short course) or moderate (asthma worse and steroid short course) disease (Table 5).

Events of particular interest

Of the 32 events for conditions known to have iatrogenic etiology, e.g. anaphylaxis, none were considered to be related to inhaler exposure. There were no reports of paradoxical bronchospasm. There were no adverse outcomes related to exposure to either Ventolin inhaler amongst the 197 reported pregnancies [Craig-McFeely et al. 2001. On the information available, none of the 144 deaths were related to treatment with either Ventolin inhaler or deterioration in disease control following inhaler transition.

Reasons for discontinuation

1,215 patients stopped their Ventolin inhaler (991 Ventolin MDI and 224 Ventolin Evohaler) commonly by generic substitution or stopping altogether. Twenty-five patients stopped Ventolin Evohaler due to trivial adverse effects, 13 of which were related to the oropharynx and previously noted in clinical trials.

Discussion

This study was the largest post-marketing observational study to monitor the transition from a chlorofluorocarbon to an hydrofluoroalkane MDI. The detailed and repeated questionnaires, comprehensive follow-up and quarterly analysis made this a robust design to rapidly detect safety signals as we monitored the launch of Ventolin Evohaler in General Practice in England. The study population was representative of the total population of regular users of Ventolin MDI enrolled at baseline and remained so throughout the study. There was preferential selection of asthmatic patients but no influence on patients' clinical care, choice of inhaler once Ventolin MDI became unavailable or reporting of outcome. 94% of the patients were prescribed Ventolin for asthma with a severity pattern similar to another community study [Rabe et al. 2000]. The GP classification of severity was consistent with other markers of severity recorded on the baseline questionnaire Our design was the most appropriate to monitor the safety of Ventolin Evohaler in normal clinical use. Spontaneous reporting of adverse drug reactions has low response rate [Heely et al. 2000]. Also a randomized clinical trial would not have provided data as rapidly nor would inclusion of the whole range of patients normally seen by GPs have been likely [Juni et al. 2001].

The primary analysis showed some events were more common in the fifth period (52.7% of the population reported by GPs to have been exposed to Ventolin Evohaler) compared to the first period (all exposed to Ventolin MDI). The most common events being respiratory tract infection and asthma worse. These followed a seasonally increased event rate in the autumn and winter months previously observed [Fleming et al. 2000]. After correcting for under-reporting, by an estimate of what we considered to be a "familiarization" effect derived from the validation study, these differences were no longer significant. However, considering the limitations of adjusting for under-reporting on the basis of the validation data on 412 patients (5.6% of the study population), both adjusted and unadjusted rates are included. Moreover, serious outcomes indicating a worsening of disease control following the introduction of the Ventolin Evohaler did not increase during the

course of the study. There were no reports of serious adverse drug reactions, causes of death or adverse pregnancy outcome attributed to Ventolin Evohaler use. That only 13 patients stopped Ventolin Evohaler due to an oropharyngeal adverse events was surprisingly small considering that GPs and pharmacists were advised to inform patients they may experience a slightly different taste, sound or feel with the Ventolin Evohaler [Liddell 1998]. These findings together with the pattern of events over time suggest that seasonality and increased accuracy of GPs' event reporting as the study progressed were the likely reasons for the event rate differences shown in the primary analysis.

The secondary analysis comparing event rates during the final period in patients exposed to Ventolin Evohaler or Ventolin MDI showed an increased crude rate for some respiratory events in the Ventolin Evohaler group. Further stratification by severity of indication showed this increase was in the broad bands of mild and moderate disease. Analysis of the rates of transition to Ventolin Evohaler by severity of indication showed a faster transition to Ventolin Evohaler in patients with more severe disease. Clinical experience would also suggest this as patients with worse asthma would request a replacement inhaler more frequently and prompt a prescription for Ventolin Evohaler. Therefore, the increased event rate in the Ventolin Evohaler group may have been due to these patients having more severe disease within each severity band.

The main limitations of this study include misclassification of exposure, under-reporting of outcomes and the smaller than expected number of patients reported to have been transitioned to Ventolin Evohaler by the end of the study. Exposure to either Ventolin MDI or HFA-Ventolin Evohaler was determined by the GPs prescription. Patients may also have had HFA and CFC inhalers in use at any one time. This determination of patient exposure may explain the difference between the reported 52.7% of the study population using Ventolin Evohaler compared to sales figures (from the manufacturer) through community pharmacies of above 80% by the end of the fieldwork. The lower than expected usage together with the under-reporting of events of all severity are weaknesses of the primary analysis. However, there was no evidence to suggest differential under-reporting between Ventolin Evohaler and Ventolin MDI. This effect increased the relevance of the secondary analysis.

Our study followed a large community population of users of a formulation of CFC salbutamol as it transitioned to an HFA formulation whilst receiving routine clinical care from general practitioners in England. Whilst it is not possible to rule out a causal relationship with rarer adverse events which our study could not detect, we did not detect the occurrence of any important safety signal primarily attributable to the HFA formulation after the introduction of Ventolin Evohaler in England.

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Conflict of interest: GlaxoSmithKline provided a grant to the Drug Safety Research Unit to conduct the study. Dr. S.A.W. Shakir worked as an employee for GlaxoWellcome between 1994 and 1997.

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