

Ng GSK Medicine: Fluticasone propionate/salmeterol, fluticasone propionate/salmeterol/norflurane
Study No: WWE113642/EPIP181/EPI40067
Title: A modified prescription-event monitoring study to assess the introduction of Seretide Evohaler™ into general practice in England
Rationale: Monitoring was required for the introduction of non-chlorofluorocarbon (CFC) propellants in metered dose inhalers (MDIs) to ensure that there were no unexpected adverse events due to the new products. A postmarketing observational study was conducted to evaluate the introduction of the MDI Seretide Evohaler™ (hydrofluoroalkane-134a inhaler containing salmeterol and fluticasone propionate).
Objectives: The aim of the modified prescription event monitoring (PEM) study was to compare event rates during the three months prior to and three months after the introduction of Seretide Evohaler™
Indication: asthma
Study Investigators/Centers: Drug Research Surveillance Unit (DSRU), Southampton, UK
Research Methods:
Data Source: Primary data collection
<p>Study Design: A modified prescription-event monitoring (PEM) study was conducted. PEM is a non-interventional cohort technique in which patients are identified from dispensed National Health Service (NHS) prescriptions written by GPs in England. This study differed from the standard PEM methodology by designing questionnaires to gather information on the pre-and post-exposure periods which allowed a comparison of 3 months before and 3 months after patients started Seretide Evohaler™. Dispensed prescriptions for Seretide Evohaler™ were identified for patients issued the drug between June 2000 and April 2001.</p> <p>Questionnaires were posted to the prescribing doctor approximately 6 months after the DSRU was notified of the first prescription for an individual patient. Study cohorts were formed from those patients for whom the GP had returned a questionnaire containing relevant information. The questionnaires requested information on demographic and disease severity characteristics of the identified individual, a report on any medical events during the three months prior to the first prescription of <i>Seretide Evohaler</i>, and a report on any medical events during the three months after the first prescription of <i>Seretide Evohaler</i>.</p>
<p>Study Population: Participants were identified by the DSRU using prescription information provided by the National Health Service Prescription Pricing Authority (PPA) of medication dispensed from the pharmacy. The DSRU identified incident (first time) prescriptions. Patients with repeat prescriptions of <i>Seretide Evohaler</i> were only included for the first prescription. Patients were included in the study if the GP indicated that they had used the medication and were registered at the practice in the post-launch time period.</p>
<p>Study Exposures, Outcomes:</p> <p>GPs were asked to report reasons for stopping if the inhaler had been stopped, suspected adverse drug reactions (ADRs) and events 3 months prior to and 3 months following the first prescription for the study drug. GPs were also asked to report any events that occurred within an hour of taking the study medications. The term 'event' was defined as, Including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in their chest disease or a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter the patients' notes.</p> <p>Reasons for stopping treatment and suspected ADRs were reviewed in detail. Where further information on selected events was required additional information was also sought on the outcome of pregnancies, and deaths where the date or cause was not specified. Deaths were ascertained by obtaining the lifetime medical records and death certificates of patients when necessary.</p>
<p>Data Analysis Methods: Incidence densities (IDs) were calculated for a given time period for all events during treatment for patients for whom either the date of stopping the drug was known or who continued to take it until the end of the 3-month exposure period. IDs were calculated for all events that occurred in the first month after starting treatment (ID₁) for the second and third months after starting treatment (ID₂₋₃), for the overall treatment</p>

period (ID_T) and for the 3-month baseline period (ID_B). Results were presented as ID per 1000 patient-months of treatment. The difference between the proportion of patients with events (and 95% confidence intervals) in the pre- and post-exposure periods was calculated using STATA (StataCorp). To compare events pre-and post-exposure incidence density ratios (IDRs) with 95% CIs were calculated using a Poisson rate model. IDRs were calculated for ID₁/ID_B, ID₂₋₃/ID_B and ID_T/ID_B. A matched-cohort analysis was conducted to compare the use of oral corticosteroids and hospital admissions between the pre- and post-exposure periods.

Limitations: Sixty-two percent (62%) of the posted Seretide Evohaler™ questionnaires were returned, which could have created a selection bias if the patients from GPs that did not participate differed from those who did participate. In general, it is possible that studies using the PEM study could lead to underreporting or over-reporting of serious and fatal adverse events. Because asthma symptoms can vary with season of the year, one would expect an increased reporting for post-exposure period during autumn or winter; however, in the study it was noted that respiratory events associated with deterioration of disease were reported less frequently in the post-exposure period. Long-term effects of the medicine were not the main focus of the study.

The incidence densities used in this study were crude and not adjusted for possible confounders such as severity of disease, season, smoking history, or age.

There was particular interest in detecting major events immediately after using *Seretide Evohaler*, namely 'paradoxical bronchospasm' or similar. It should be noted that this methodology is not the ideal to detect paradoxical bronchospasm. The GP was therefore specifically asked whether he/she was aware of any events occurring immediately (within approximately one hour) after use of *Seretide Evohaler*.

Study Results:

The study cohort consisted of 15, 756 patients with valid questionnaires returned from 25,432 questionnaires originally sent. (Table 1). There were more females (52.2%) than males (44.3%). At the time of marketing, Seretide Evohaler™ was only recommended for children aged ≥12, and 6.1% of the cohort were aged younger than 12 years. During the study period, asthma was the only licensed indication for Seretide Evohaler™ and this was listed as the primary indication for 83.5% of the patients; COPD was listed as a primary indication or for part of the indication for 13.8% of patients.

Table 1. Information on the Seretide Evohaler™ cohort

Cohort data	Number
Questionnaires sent	25432
Questionnaires returned and entered (% forms sent)	15756 (62.0)
Void (% forms returned and entered)	2292 (14.5)
Eligible and valid returned questionnaires (% forms sent)	13464 (52.9)
Male (% cohort)	5959 (44.3)
Female (% cohort)	7033 (52.2)
Sex not specified (% cohort)	472 (3.5)
Median age (years) males (interquartile range, IQR)	55 (33-71)
Median age (years) females (IQR)	54 (35-70)
Age not specified (% eligible cohort)	825 (6.1)

Oral corticosteroid prescription is a marker for deterioration in asthma control or worsening of asthma symptoms; therefore, it was important to evaluate variation in oral corticosteroid use after the introduction of Seretide Evohaler™. During the study, 27.9% required one or more courses of oral corticosteroids. There was no evidence of an increase in the use of oral corticosteroids in the exposure period compared to the pre-exposure period; rather there was a trend toward decreased use during the exposure period (Relative Risk (RR)=0.95, 95% CI: 0.90, 0.99), particularly for patients classified by the GP as having mild or moderate asthma (Table 2). For hospital admissions, no clear differences were observed for the rates pre- and post-exposure for the overall population or by severity.

There were 33 events reported as suspected adverse drug reactions (ADRs) in 30 patients. Eight of the suspected ADRs were reported to have occurred within an hour of using Seretide Evohaler™, one event each of: headache, chest pain, palpitations, cough, breathlessness, increased shortness of breath/wheeze in an asthmatic, choking and faintness, and stiffness and tingling with paraesthesia of fingers. The remaining events reported were consistent with the labelled adverse-effect profile for Seretide Evohaler™: muscle cramps, headache, palpitations, hoarseness, sore mouth, and oral candidiasis.

The ten most commonly reported adverse events are shown as counts by month in Table 3 and as incidence densities (IDs) and incidence density ratios (IDRs) in Table 4. When the first month of exposure (ID₁) was compared to the period prior to exposure (ID_B), 'asthma worse', 'cough', 'COPD', and 'asthma/wheezing' were all reported less frequently in the first month of exposure than in 3 months prior to starting Seretide Evohaler™. These events as well as lower respiratory tract infections, dyspnoea, and 'non-surgical admissions' were all reported less frequently during the entire treatment (ID_T) period compared to baseline period prior to using Seretide Evohaler™ (ID_B). The events reported significantly more frequently during the first month of exposure (ID₁) compared with baseline (ID_B) were 'intolerance' (ID₁/ID_B 39.59, 95% CI: 9.91, 344.2), 'palpitation' (ID₁/ID_B 2.47, 95% CI: 1.22, 4.91), 'cramp' (ID₁/ID_B 2.24, 95% CI: 1.04, 4.72) and 'malaise/lassitude' (ID₁/ID_B 1.84, 95% CI: 1.12, 2.98).

During the study period there were 64 patients (0.5%) who had one or more events within an hour of using Seretide Evohaler™. Of these, 39 were followed up for further information, no replies were received for 12 patients and a blank questionnaire was returned for four patients. A case of 'paradoxical bronchospasm' was reported to have occurred within an hour of using Seretide Evohaler™ and assessed as possibly related to treatment. Another patient was reported to have 'bronchospasm', which was followed up; however, no further information was received.

One case of allergy was classified as possibly related to Seretide Evohaler™; it was described as puffy itchy eyes and occurred approximately 1 month after starting Seretide Evohaler™ in the winter.

There were 59 pregnancies reported in the 3 months pre- and 3 months post-exposure to Seretide Evohaler™, with 41 known to have been exposed to Seretide Evohaler™. Outcomes of these pregnancies were reported for 38 patients, including: 30 live births, four spontaneous abortions, one missed abortion, and three elective terminations of pregnancy. Of the 15 pregnancies exposed during the first trimester with a known birth outcome, 12 were born at term and three had unknown timing.

There were 52 deaths reported in the 3-month exposure period, 39 of whom were reported to have been taking Seretide Evohaler™ at the time of death; two were not taking Seretide Evohaler™ and for 11 exposure timing was not known. The cause of death was obtained for 38 patients: 18 cardiovascular causes, 11 respiratory causes, 8 cancer, and 1 pancreatitis. None of the respiratory deaths were attributed to asthma; however six deaths were attributed to COPD. With the exception of cystic fibrosis patients who died from respiratory causes, all were older than age 60 years.

Table 2. Relative risk of oral corticosteroid use and hospital admissions in the pre- and post-exposure periods, stratified by disease severity

	Pre-exposure [n, (%)]	Post-exposure [n, (%)]	Relative risk [95% CI]
Corticosteroid use			

Mild	122 (0.9)	101 (0.8)	0.83 [0.66, 1.04]
Moderate	1436 (10.7)	1291 (9.6)	0.90 [0.84, 0.96]
Severe	765 (5.7)	803 (6.0)	1.05 [0.97, 1.13]
Total	2332 (17.3)	2206 (16.4)	0.95 [0.90, 0.99]
Hospital admissions			
Mild	5 (<0.1)	6 (<0.1)	1.20 [0.41, 3.51]
Moderate	107 (0.8)	91 (0.7)	0.85 [0.66, 1.10]
Severe	112 (0.8)	98 (0.7)	0.88 [0.69, 1.12]
Total	225 (1.7)	196 (1.5)	0.87 [0.73, 1.04]

Table 3. The ten most commonly reported adverse events prior to and during treatment with Seretide Evohaler™, number of events

Higher term	Events During exposure to Flixotide Evohaler™				Events Prior to exposure
	Month 1	Month 2	Month 3	Total of 3 months	Total of 3 months
Asthma worse	313	218	191	722	1584
Respiratory tract infection, lower	302	275	240	817	1024
Respiratory tract infection, upper	206	227	186	619	630
Cough	112	61	66	239	424
Hospital referrals, no admission	93	72	54	219	218
COPD	85	73	68	226	339
Dyspnoea	74	31	38	143	293
Non-surgical admissions	69	52	46	167	225
Asthma, wheezing	66	30	28	124	344
Pain, joint	41	35	38	114	121

Table 4. The ten most commonly reported adverse events during treatment with Seretide Evohaler™, incidence densities (IDs) and incidence density ratios.

Higher term	During exposure to Seretide Evohaler™				Prior to exposure
	ID ₁	ID _T	ID ₁ /ID _B (95%CI)	ID _T /ID _B (95%CI)	ID _B
Asthma worse	23.60	18.82	0.60 (0.53, 0.68)	0.48 (0.44, 0.52)	39.22
Respiratory tract infection, lower	22.77	21.30	0.90 (0.79, 1.02)	0.84 (0.77, 0.92)	25.35
Respiratory tract infection, upper	15.53	16.14	1.00 (0.82, 1.17)	1.04 (0.92, 1.16)	15.60
Cough	8.45	6.23	0.80 (0.65, 0.99)	0.59 (0.50, 0.70)	10.50
Hospital referrals, no admission	7.01	5.71	1.30 (1.01, 1.66)	1.06 (0.87, 1.28)	5.40
COPD	6.41	5.89	0.76 (0.59, 0.97)	0.70 (0.59, 0.83)	8.39
Dyspnoea	5.58	3.73	0.77 (0.59, 1.00)	0.51 (0.42, 0.63)	7.25
Non-surgical admissions	5.20	4.35	0.93 (0.70, 1.23)	0.78 (0.64, 0.96)	5.57
Asthma, wheezing	4.98	3.23	0.58 (0.44, 0.76)	0.38 (0.31, 0.47)	8.52

Pain, joint	3.09	2.97	1.03 (0.71, 1.48)	0.99 (0.76, 1.29)	3.00
<p>ID, incidence density of event; ID₁, incidence density of event for 1st month post-exposure to Seretide Evohaler™; ID_T, incidence density of event for months 1 to 3 post-exposure to Seretide Evohaler™; ID_B, incidence density of event for months 1 to 3 pre-exposure or baseline.</p>					
<p>Conclusion: See publication below.</p>					
<p>Publications: Perrio MJ, Wilton LV, Shakir SA. A modified prescription-event monitoring study to assess the introduction of Flixotide Evohaler™ into general practice in England: an example of pharmacovigilance planning and risk monitoring. <i>Pharmacoepidemiology and Drug Safety</i> 2007;16:960-978.</p>					

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