

# A Prescription Event Monitoring (PEM) Study To Assess Safety And Health Outcomes Of Salmeterol And Fluticasone Propionate (Airtec SF®) For Partly/Uncontrolled Asthma In Indian Population

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## Citation

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## Abstract

**Background:** Asthma management has been fraught with several challenges especially for partly or uncontrolled cases. Incremental dosage strategy with Salmeterol, Fluticasone propionate combination offers stable yet effective control of symptoms preventing further exacerbations. However there is limited evidence available on the need and safety profile of this incremental dosage strategy with the combination especially in Indian settings

**Objective:** To examine the safety and adverse clinical outcomes of Airtec SF® when prescribed in patients with well- or poorly controlled persistent asthma.

**Material and Methods:** Based on the principle of Prescription Event Monitoring (PEM) for safety reporting, this study was conducted at 20 centers across India. PEM study booklets with study questionnaire were provided to capture information related to adverse 'Events' during the observation period of 30 days.

**Results:** 384 patient records were analyzed, mean age 44.5 years of which 48% were male and 52% were female. 150 (39%) were newly diagnosed, 144 (61%) were partly controlled and 90 (38%) had uncontrolled asthma. They were prescribed with MDI (n=124) or DPI (n=110) of Airtec SF® with most receiving aggressive dosing strategy of 2 puffs or inhalations twice daily (table 1). Dosing consistency was maintained by 92% and 100% cases receiving high doses of Airtec SF® as MDI or DPI formulations respectively. Adverse events (3%) noted included infective pneumonitis or upper respiratory tract infection (URTI) that were mild to moderate intensity and treated symptomatically. Among the deescalated group, none of the patients required treatment discontinuation due to adverse events.

**Conclusion:** Airtec SF® was safe and well tolerated amongst partly or uncontrolled asthma patients. Initiation of Airtec SF\* in high doses for these patients resulted in low incidence density for the first month (Low LD1).

## INTRODUCTION

Bronchial asthma continues to be a major cause for morbidity and mortality worldwide with prevalence increasing in most of these countries. The current management of Bronchial asthma is fraught with several challenges especially in light of recent evidence for increased exacerbation rate with its indirect impact for impaired quality of life. There is compelling evidence available indicating that the combination of low or moderate doses of inhaled corticosteroids (ICS) along with long-acting

β<sub>2</sub>-agonists (LABA) improves asthma control in adults also reduces the rate of exacerbations [1]. The combination of ICS + LABA for maintenance therapy is recommended strongly in asthma treatment guidelines for the treatment of moderate to severe asthma [2]. OPTIMA and FACET studies have shown that there is remarkable improvement in asthma control using low doses of ICS/LABA combination. The safety profiles of fluticasone propionate and salmeterol are well established, as the products have been well established, though few adverse effects have been reported

like hoarseness, candidiasis, headache, tremor, and palpitations have been reported [3]. However despite the availability of these standardized therapies, most the patients do not have well-controlled asthma

The recent updated GINA guidelines for Bronchial asthma have therefore risk stratified these patients as 'Partly' or 'Uncontrolled' asthma while advocating 'Step-Care' approach for them involving high-dose ICS/LABA combination along with/without xanthine inhibitors or leukotriene receptor antagonists

A PEM study was therefore conducted to evaluate the safety profile of ICS/LABA or Salmeterol/Fluticasone (Airtec SF®) in partly or uncontrolled asthma using 'Differential' dosing strategy in real-world clinic settings of India.

## MATERIALS AND METHODS

PEM is a well-established, non-interventional, observational tool of pharmacovigilance to evaluate the safety profile of the prescribing drugs in 'real world clinic settings' [4]. 'Events' information related to safety or any adverse health outcomes is usually captured with immediate notification of any serious adverse events.

Newly diagnosed or currently risk stratified poorly controlled asthmatic patients as Partly or Uncontrolled asthma who were placed on Salmeterol-Fluticasone combination (Airtec SF®) inhalation therapy via MDI or DPI were observed for any adverse health outcome or side effects during the observation period of 60 days. Asthma Control status was assessed as per risk stratification suggested by GINA (2014) as partly- or uncontrolled asthma.

PEM questionnaire were distributed among the clinicians seeking details of the patients at baseline day i.e. Day 0 and follow-up details were filled up on Day 30 and 60 respectively.

All the details including asthma control need of concomitant medications, and requirement of rescue medications, hospitalization along with adverse events during the observation period were noted.

During the observation period, each patient was observed for any 'events' that may arise following prescription for Airtec SF\* (Salmeterol-fluticasone) thereof that noted in PEM Report form and notified immediately to Sponsor Pharmacovigilance center in case of Serious Adverse events

including death, disability, hospitalization or congenital anomaly. At the end of the observation period, the PEM booklets were collected. Based on the safety profile or observations with the drug, additional follow-up was done with the prescribing doctors for confirmation and causality assessment based on the pharmacological properties, concurrent disease or drug use.

The results were analyzed using Descriptive statistics,

## RESULTS

This PEM was conducted at 20 centers across India. Records of 384 patients, predominantly as males (58%) and mean age of 44.5 yrs with follow-up data for 30 days observation period were available for analysis

**Table 1**

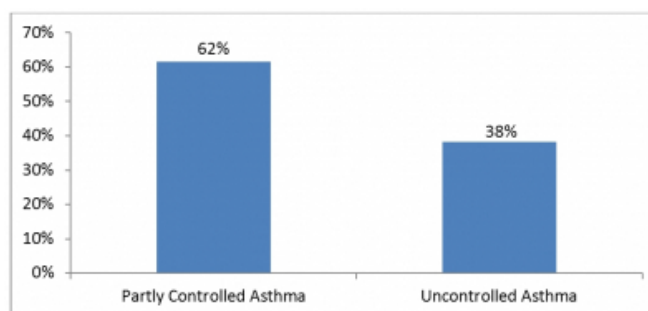
Baseline Demographic Data

Patient pool	384
• Male	221
• Female	163
• Age (Mean)	44.5 yrs
<b>Asthma Control Status</b>	
• Newly Diagnosed Patients	150
• Partly Controlled Asthmatics	144
• Uncontrolled Asthmatics	90

Baseline Symptoms: Most of the patients presented with daytime symptoms (>2 times/wk) in 81% cases unlike nocturnal occurrence (57%). Overall the patients were risk stratified as Partly or Uncontrolled asthma in 62% and 38% cases respectively as shown in figure 1

**Figure 1**

Baseline Asthma Control Status



Co-morbid conditions: Careful history of the patients Revealed that more than half of the patients, (56%) were suffering from allergic rhinitis; followed by history of cardiovascular diseases, hypertension or Type 2 DM.as

highlighted in table2.

**Table 2**

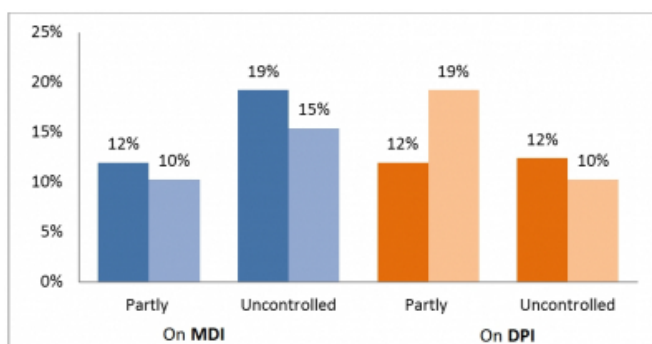
Clinical comorbidities noted at baseline visit

Clinical Comorbidities	% (n)
• Allergic Rhinitis	56% (216)
• Cardiovascular disease	32% (123)
• Type 2 Diabetes	9% (33)
• GERD	6% (22)
• Obstructive Sleep Disorder	5% (19)
• Others	3% (10)

In most of these partly or uncontrolled asthma patients, MDI was preferred as common route of drug delivery as highlighted in Fig 2

**Figure 2**

Baseline Patient disposition chart



In both the group of patients ie. Partly or Uncontrolled cases, Airtec SFC® was suggested to be administered in high dosages delivering fluticasone propionate at a daily dose of 1000 mcg (Table 3)

**Table 3**

Dose Strategy for moderate-severe asthma patients during the study

Airtec SF MDI 250/25 mcg				
	1 Puff b.i.d		≥2 Puff b.i.d	
	Baseline	30 Days	Baseline	30 Days
Partly Controlled	0	7	46	39
Uncontrolled	1	1	42	42
Total	1	8	88	81

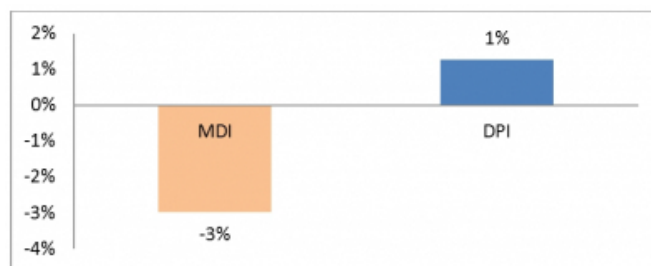
  

Airtec SF DPI 250/50 mcg				
	1 Inhalation b.i.d		≥2 Inhalation b.i.d	
	Baseline	30 Days	Baseline	30 Days
Partly Controlled	19	17	27	29
Uncontrolled	14	13	10	11
Total	23	30	37	40

In the group of patients who were initiated with aggressive dosing i.e. (≥2 puffs) dose titration was observed both in MDI and DPI group as shown below in figure 3

**Figure 3**

Overall Dose Titration in MDI and DPI group



Adverse Events: Eighteen adverse events were observed during the study. Most of them including GERD and Respiratory tract infections (RTIs) were mild requiring symptomatic treatment (Table 4)

**Table 4**

Adverse events at the end of follow-up visit (Day 30)

Adverse Event	Total (n)
Exacerbation	8
LRTI	4
URTI	2
Fever	1
Total	15

While none in the newly diagnosed group of asthma patients

reported exacerbations, eight cases (3.4%) in the partly or uncontrolled subgroup had these episodes at the end of 30 day follow-up visit with five of them requiring hospitalization.

## **DISCUSSION**

Goal of asthma therapy remains optimal control so that patients can live active, full lives while minimizing their risk of exacerbations and other issues including side effects leading to treatment non-adherence. A step-care approach involving graded dosages of ICS/LABA combinations has been recommended for newly diagnosed patients while offering optimal Control in patients with partly- or uncontrolled asthma

Salmeterol/fluticasone propionate dry powder inhaler (DPI) or metered-dose inhaler (MDI) as a standardized maintenance therapy has often been recommended in the management of moderate to severe asthma [5]. Several studies have established that salmeterol and fluticasone propionate combined in a single dry powder inhalation device are at least as effective as a combination of the 2 drugs administered via separate dry powder inhalers and more effective than monotherapy with fluticasone propionate or budesonide [6] while improving long-term patient compliance to therapy as highlighted by the landmark trials of GOAL, EXCEL, CONCEPT [8,9,10]

PEM remains a simple observational tool to evaluate the safety and adverse health outcome especially in 'real world' clinic settings.

The current study highlighted the distinctive safety profile of ICS/LABA combination ie. Salmeterol/Fluticasone especially with High-dosage strategy of fluticasone propionate in 99% and 61.6% cases on MDI or DPI respectively. This aggressive dosing strategy was again maintained amongst the partly-& uncontrolled asthma patients in 92% & 100% of the cases on MDI or DPI respectively with no treatment withdrawals due to side effects

Side effects noted during the study were of mild to moderate intensity with most of them treated symptomatically. Seven cases (3%) of upper/lower respiratory infection and pyrexia were managed symptomatically with oral antibiotics and did not require any indoor admission for further management. The results can be positively correlated with the EXCEL study wherein, drug related adverse events were noted in

<10% cases with nearly half of them related to hoarseness or dysphonia due to drug deposition in oral cavity amongst newly diagnosed patients with moderate to severe asthma

Similarly, Exacerbations were noted in eight (3.4%) patients with five of them requiring treatment for secondary bacterial infection or pneumonitis with oral antibiotics/short course oral corticosteroid therapy. In the other cases, poor patient compliance and accidental exposure to dust and smoke were cited as the confounding variables. Other landmark trials including EXCEL (n=694) and CONCEPT (n=344) observed exacerbation rates of 10% and 11.3% respectively [7,9,10] but were limited by 'fixed dosing' strategy for patients not currently assessed as per their Asthma Control status

The current study represents first of its kind clinical documentation for salmeterol and fluticasone combination especially in patients with partly and uncontrolled asthma while showcasing the therapeutic benefits of aggressive dosing strategy in these difficult-to-treat asthma cases. This would however require further validation as a randomized, multi-centric clinical trial to support the above dosing strategy while risk stratifying the patients based on their Asthma Control status as highlighted by the recent updated GINA guidelines [2]

## **CONCLUSION**

Uncontrolled asthma often represents a clinical dilemma with several factors related to drug, device or patient compliance for consideration. The ensuing complications as 'Exacerbation/s' are often associated with high morbidity

The current PEM demonstrated use of Airtec SF as safe and well tolerated option with negligible rate of exacerbations in Indian population especially amongst poorly controlled asthma patients.

## **ACKNOWLEDGEMENT**

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## **DISCLAIMERS**

The authors have published a similar abstract previously,

which can be found here:

<http://www.scopemed.org/?mno=171672>

However this article is a subgroup analysis with completely rewritten text.

Also, the authors are associated with Glenmark Pharmaceuticals. ISPUB did not receive any additional compensation for publishing this article.

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