Safety of Fluticasone Furoate Nasal Spray Among Filipino Patients with Allergic Rhinitis: A Post-Marketing Surveillance Study

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Abstract

Introduction: Allergic rhinitis (AR) is a highly prevalent chronic disease affecting up to 30% of the population worldwide.[1] Although AR is not life-threatening, it greatly impacts patients' health-related quality of life and furthermore, if left untreated, it may be complicated by other respiratory co-morbidities.[2] Intranasal corticosteroids are one of the several classes of medications recommended to manage AR. Fluticasone furoate nasal spray is a novel enhanced-affinity glucocorticoid for the management of AR.[2] This study assessed the safety profile of Fluticasone furoate nasal spray in the treatment of Filipino patients with AR.

Methods: This is a multicenter, prospective, post-marketing surveillance study aimed at documenting adverse events, their frequency and severity as assessed by the investigators among Filipino patients with AR administered with Fluticasone furoate nasal spray from August 2010 to January 2013.

Results: Four hundred thirty-nine (439) patients were enrolled in the study. Among these, 421 patients were included in the safety analysis population. Eighteen patients were excluded from the safety analysis population due to protocol violation and lack of post-baseline safety assessment. Of the total eligible population, 10 patients (2.4%) experienced adverse events (AEs) with a total of 10 and no serious adverse events (SAEs) were reported. Eight of these 10 AEs resolved while two AEs had unknown outcome. One patient (0.2%) experienced an AE suspected to be related to study medication. The most common AE occurring in eight patients was respiratory-related which were nasal dryness (3 events), rhinorrhea (2 events), epistaxis (1 event), nasal discomfort (1 event) and rhinalgia (1 event).

Conclusion: Fluticasone furoate nasal spray, among indicated patients with AR showed AEs which approximate AE of other similar post-marketing studies with incidence of less than 1% for each event.(21) Neither SAEs nor drug-related deaths were reported throughout the study.

Keywords: fluticasone furoate nasal spray, allergic rhinitis, filipino

Introduction

Allergic Rhinitis (AR) is a highly prevalent chronic disease affecting up to 30% of the population worldwide, including US, Europe and Asia.[1] Although AR is not a life-threatening disease, it greatly impacts patients' health-related quality of life and furthermore, if left untreated may be complicated by other respiratory co-morbidities.[2] It is the most chronic condition in children[3], with onset at eight to 11 years of age but occurs in people of all ages. It affects boys more than girls in childhood but affects the sexes nearly equally in adulthood.[4] In 2008, the overall prevalence of AR among Filipino adults is 20.0%.[5]

Allergic Rhinitis is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the nasal membranes. Symptoms include rhinorrhea, nasal obstruction, nasal itching and sneezing.[6] Ocular symptoms such as redness, tearing or itching may also be present.[7] It can be complicated by co-morbidities including asthma, sinusitis and otitis media.[8] Symptoms disturb sleep, cause fatigue and impair concentration causing negative effects on productivity and quality of life.[9]

Several classes of medications, including intranasal corticosteroids, oral and intranasal antihistamines, decongestants, and intranasal anticholinergics and mast cell stabilizers are available to manage AR. Of these classes of pharmacotherapy, only intranasal corticosteroids have proven anti-inflammatory activity against pathophysiological aspects of both early- and late-phase allergic reactions and have a broad spectrum of efficacy for the range of nasal symptoms including congestion, rhinorrhea, sneezing, and nasal itching.[2,10,11] Accordingly, intranasal corticosteroids are considered the first line of therapy when nasal congestion is a major component of AR.[12]

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and the local Philippine Society of Allergy, Asthma and Immunology Guideline recommend that patients with

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moderate to severe disease receive intranasal corticosteroid as first line therapy.[6,13] Intranasal corticosteroids provide potent anti-inflammatory activity locally at the nasal mucosa while limiting systemic corticosteroid exposure.[14]

Fluticasone furoate is a synthetic, lipophilic trifluorinated glucocorticoid receptor agonist containing a 17α-furoate ester.[15] It is a novel topical, intranasal corticosteroid with enhanced affinity for the glucocorticoid receptor and low systemic exposure, developed for the treatment of AR.[16] In in vitro studies with human bronchial epithelial cells, fluticasone furoate showed slow flux across cellular membranes but incorporated easily into the cells.[15] In studies in healthy volunteers, fluticasone furoate nasal spray given as single and repeated intranasal doses of up to 800 ug was well tolerated and associated with very low systemic exposure; the majority of plasma concentration measurements were less than the lowest quantifiable concentration.[17]

This post-marketing surveillance study was principally undertaken to document the clinical experience on the use of fluticasone furoate nasal spray among Filipino patients with AR. Specifically, this study aims to assess the safety profile of fluticasone furoate in the treatment of Filipino patients with AR.

Methods

This is a multicenter, prospective, post-marketing surveillance study aimed at documenting adverse events, their frequency and severity as assessed by the investigators among Filipino patients with AR administered with fluticasone furoate nasal spray from August 2010 to January 2013.

Inclusion and exclusion criteria

Patients who were eligible for inclusion in the study met ALL of the following criteria: Patients (pediatric starting at two years old and above; and adults) with clinically diagnosed AR.; provided written informed consent to take part in the study (for pediatric patients, the parent or legal guardian should give the consent); currently prescribed or being treated as per recommendation of fluticasone furoate nasal spray prescribing information.

On the other hand, patients were excluded from the study if hypersensitivity to fluticasone furoate or any component of the preparation is evident.

Drug preparation, dosage, and administration

Fluticasone furoate (Avamys™) is a topical, intranasal enhanced affinity trifluorinated glucocorticoid with potent anti-inflammatory activity and low systemic exposure.[16] It comes in a nasal spray, as an aqueous suspension of micronized fluticasone furoate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. Each actuation delivers 27.5 ug of the drug in a volume of 50 uL of suspension that also contains 0.015% weight per weight benzalkonium chloride, dextrose anhydrous, edentate disodium, microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80 and purified water.[18] The recommended dosage of fluticasone furoate nasal spray is 55 ug for children ages two to 11 years of age and 110 ug for adults and adolescents ages 12 years and older at once daily dosing.[19]

The physician's decision regarding AR proper treatment and care was prescribed in the standard of care and made in the course of normal clinical practice. The investigators were made aware of the full prescribing information of fluticasone furoate nasal spray. Treatment administration, patterns, and changes were at the discretion of the investigators and were dependent on the clinicians' judgment. There was no attempt to influence the prescribing patterns of any individual investigator. Only patients who were prescribed with and used fluticasone furoate nasal spray were included in the study. The study drug was not provided by the study sponsor.

Data collection

This study was conducted from August 2010 to January 2013. Informed consent was obtained from each individual or decision maker or their parents/guardians for minor patients, prior to being eligible for inclusion in the study. At the beginning of the study, participants were informed that they may withdraw from the study at any point for any reason or upon their physicians' prerogative.

There were at least two patient visits. On the first visit, the following were required information: informed consent, demographic data including weight, height, date of birth, sex and race, physical examination, assessment of patient eligibility according to approved fluticasone furoate nasal spray prescribing information, medical history, concomitant medications and laboratory data (if any).

Patient returned for follow-up visit after the initial visit. The visit timeline was two weeks or as appropriate upon the judgment of the clinician. On the second visit, the following were obtained and recorded: assessment of AE, assessment of compliance, concomitant medications/ treatments, laboratory tests (if any).[4]

Data analysis and sample size determination

Demographic and baseline characteristics were collected from all patients included in the safety analysis population. For continuous data, descriptive statistics such as mean, standard deviation, median, minimum and maximum, were computed. On the other hand, frequencies

and percentages were computed for categorical data. Percentages were calculated based on the safety population with non-missing data.

The regulatory requirement of the Food and Drug Administration (FDA) Philippines for Post-Marketing Surveillance Studies is a sample size of 3,000 patients over a period of three years or 10% of the total marketing projection for this study drug for the three years of monitored release. Redefining how post marketing surveillance will be conducted, the FDA has requested all ongoing studies to be discontinued by December 2012. The total enrollment was stopped at 439 at the time of the discontinuation.

Results

Four hundred thirty-nine (N=439) patients were enrolled in the study. Among these, eighteen patients were excluded from the safety analysis population due to protocol violation and lack of post-baseline safety assessment. A total of 421 patients were included in the safety analysis population (Table I). Female patients slightly predominated at 54.9% vis-à-vis male patients at 44.6%. Three patients had missing gender data. The youngest patient included was three years old while the oldest patient was 78 years old with a median age of 32 (Table II). One hundred eleven (26.4%) patients had history of pre-existing infections (e.g. Sinusitis) and were on systemic anti-infective medications (e.g. Amoxicillin) and 193 (45.8%) patients were on respiratory system medications (e.g. Levocetirizine) (Appendix I, II).

Most of the patients (62.9%) were administered fluticasone furoate nasal spray at once-a-day dosing, and 31.1% at twice-a-day dosing. The rest at 5.7% were administered other doses. Total daily dose of 110 ug was received by 70.8% of the patients while 2.4% received 55 ug (Appendix III). Some of the patients (8.6%) changed doses due to lack of effectiveness but none of these changes was attributable to AEs. Other reasons for changing dose include significant symptom improvement and shifting to maintenance dose. Average treatment duration was 3.4 weeks with a range of 0.3 week to 105.9 weeks (Table III).

Safety evaluation

Patients who experienced AEs represented 2.4% of the total eligible population and no SAEs were reported (Table IV). Eight of these AEs were resolved while two AEs had unknown outcomes (Table VI). One patient (0.2%) experienced an AE (nasal dryness) suspected related to the study medication which caused permanent discontinuation of the study medication (Table IV). The most common AE occurring in eight patients was respiratory-related which were nasal dryness (3 events), rhinorrhea (2 events), epistaxis (1 event), nasal discomfort (1 event) and rhinalgia (1 event) (Table V).

Table I. Patients' disposition

	No. of Subjects	%
Screened patients	439	100.0
Patients who received treatment*	435	99.1
Safety population*	421	95.9
Excluded from the safety population	18	4.1
Patients with protocol violations	6	1.4
Without endpoint evaluation	8	1.8
Number of patients who completed the study*	431	98.2
Reasons for discontinuation		
Adverse/serious adverse event	1	0.2
Lack of efficacy	1	0.2
Deviation from protocol	2	0.4
Lost to follow-up	3	0.7
Termination of study by GlaxoSmithKline	0	0.0
Others	0	0.0

**The denominator used in the computation of percentages is the number of screened patients.*

Table II. Patients' demographic characteristics

	n (%)	Mean	SD	Median	Minimum	Maximum	Missing
Sex							
Male	187 (44.6)	-	-	-	-	-	3
Female	231 (54.9)	-	-	-	-	-	
Age (Years)	388	33.5	16.3	32.0	3.0	78.0	33
Height (cm)	305	158.7	12.3	160.0	91.0	183.0	116
Weight (kg)	318	59.1	15.9	59.0	5.0	135.0	103
Race							
Asian	408 (96.9)	-	-	-	-	-	13
Others	0 (0.0)	-	-	-	-	-	

**The denominator used in the computation of percentages is the number of screened patients.*

Discussion

The American College of Rheumatology (ACR) published a preliminary classification criteria to classify patients with systemic sclerosis (SSc) which showed a 97% sensitivity and 98% specificity.[2] The diagnosis is ascertained, if either one major criteria (scleroderma proximal to the metacarpophalangeal or metatarsophalangeal joints) or at least two or more minor criteria (sclerodactyly, digital ulcerations and/or pitting digital scars and bibasilar pulmonary fibrosis) are present.[3] In our case, one major criteria and two minor criteria were fulfilled (i.e sclerodactyly and digital ulcerations. She did not present with dyspnea and had unremarkable chest findings.

Fluticasone furoate nasal spray is indicated for treatment of nasal symptoms of seasonal and perennial AR in patients two to 11 years of age and treatment of nasal

Table III. Dose change and treatment duration

	n (%)*	Mean	SD	Median	Minimum	Maximum	Missing
Any dose changed?							
Yes	35(8.3)						
Increase	1						
Decrease	23						
Cannot be determined	11						
No	385 (91.4)						
Missing	1						
Treatment duration (weeks)	421	3.4	2.0	6.5	0.3	105.9	0
Final total daily dose (ug)	406	88.9	110.0	35.5	10.0	165.0	15
Reason for dose change							
Lack of effectiveness	3 (8.6)						
Adverse event	0 (0.0)						
Other	32 (91.4)						

*The denominator used in the computation of percentages is the number of screened patients.

Table IV. Overall incidence of adverse events

	No. of subjects (%*)	No. of Events
Experienced AE	10 (2.4)	10
Experienced AE related to study medication	0 (0.0)	0
Experienced SAE	0 (0.0)	0
Experienced SAE related to study medication	0 (0.0)	0
Experienced AE which cause permanent discontinuation of study medication	0 (0.0)	0
Experienced AE suspected related to Avamys which cause permanent discontinuation of study medication	1 (0.2)	1
Experienced SAE which cause permanent discontinuation of study medication	0 (0.0)	0
Experienced SAE suspected related to Avamys which cause permanent discontinuation of study medication	0 (0.0)	0

*The denominator used in the computation of percentages is the safety population.

and ocular symptoms of seasonal AR and nasal symptoms of perennial AR among adults and adolescents. It is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity.[19] This was a multicenter, prospective, post-marketing surveillance study aimed at documenting adverse events, their frequency and severity as assessed by the investigators among Filipino patients with AR administered with fluticasone furoate nasal spray.

With intranasal corticosteroids, the occurrence of systemic side effects is limited by the targeted delivery of

Table V. Incidence of AEs by medDRA term

System Organ Class	Preferred Term	Incidence No. of subjects(%*)	No. of Events (%*)
General disorders and administration site conditions		1 (0.2)	1
	Drug Ineffective	1 (0.2)	1
Nervous System Disorders		1 (0.2)	1
	Hypersomnia	1 (0.2)	1
Respiratory, Thoracic And Mediastinal Disorders		8 (1.9)	8
	Epistaxis	1 (0.2)	1
	Nasal Discomfort	1 (0.2)	1
	Nasal Dryness	3 (0.7)	3
	Rhinalgia	1 (0.2)	1
	Rhinorrhea	2 (0.5)	2
Total		10 (2.4)	10

*The denominator used in the computation of percentages is the safety population.

medication to its nasal mucosal site of action.[7,11] The low potential of intranasal corticosteroids for causing systemic side effects has been established in both short- and long-term studies.[7,11]

In a randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study on 641 patients conducted by Martin et. al in 2007, it was found that the overall incidence of AEs was similar to that of the placebo, 27% vs. 24%-29% on the different dosages as prescribed. Headache and epistaxis were the only AEs reported in greater than 3.0% of the patients in any treatment group. There was increased incidence of epistaxis with dose of fluticasone furoate (4.0% for placebo, 3% for 55 ug, 8% for 110 ug, 9% for 220 ug and 7% for 440 ug), but no increase with dose for headache. Withdrawals due to AEs during the study were low (nine patients, 1.0%). One event of pruritus in the 55-microgram group and nasal candidiasis in the 220-microgram group were the only AEs leading to premature withdrawal that were considered by the investigator to be drug-related.[9] Fluticasone furoate nasal spray had a favorable safety and tolerability profile across all four studies. Mild-to-moderate headache and epistaxis were the most common drug-related AEs. These results are not surprising because headache is commonly reported in clinical trials. Overall, rates of epistaxis were greater in the fluticasone furoate nasal spray group than in the placebo group, ranging from 2% to 8% and <1% to 4%, respectively. Nonetheless, all cases were mild-to-moderate in intensity. This is consistent with rates of epistaxis reported in other INS; a low rate of epistaxis is generally accepted to be a pharmacologically predictable effect of INS.[20]

Table IV. Outcome of AEs and relationship of AEs to the study medication

		No. of Subjects	No. of Events	%*
Outcome	Fatal	0	0	0.0
	Resolved	8	8	1.9
	Sequelae	0	0	0.0
	Unresolved	0	0	0.0
	Improved	0	0	0.0
	Worse	0	0	0.0
	Unknown	2	2	0.5
Relationship to the study medication	Yes	0	0	0.0
	No	0	0	0.0
	Probable	8	8	1.9
	Possible	1	1	0.2
	Unlikely	0	0	0.0
	Unknown	0	0	0.0
	Null	1	1	0.2
Serious at any time during the study?	Yes	0	0	0.0
	No	10	10	2.4
	Null	0	0	0.0

%-Proportion of subjects in population having adverse event
Probable: There is probably a direct cause and effect relationship between the adverse experience and the study drug.
Possible: A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.
Unlikely: There are other, more likely causes and the drug is not suspected as a cause.
Null: Relationship to the study medication was not defined by the investigator.
**The denominator used in the computation of percentages is the safety population.*

Adverse drug reactions observed in clinical trials include the following: epistaxis, ulcerations, candida albicans infection, impaired wound healing, cataracts and glaucoma, immunosuppression, hypothalamic-pituitary-adrenal axis effects including growth reduction. In one controlled clinical trial, epistaxis occurred more frequently (20%) in the group receiving fluticasone furoate nasal spray compared with the placebo group (eight percent), but this was of mild intensity in majority of the patients. Respiratory-related adverse events such as dry throat, cough, nasal discomfort and nasal dryness were commonly reported AEs with an incidence of less than one percent. In post-marketing studies, adverse events include headache, which was common. Reports of rhinalgia, nasal discomfort and nasal dryness have been uncommon.[2]

In this post-marketing study, fluticasone furoate nasal spray administration posed mild to moderate adverse events. As stated in the results, there were no SAEs reported and almost all AEs were similar to those reported in clinical trials such as epistaxis, rhinalgia, rhinorrhea and nasal dryness and discomfort. These were all of mild intensity and most of these were resolved. However, one patient discontinued from the study due to nasal dryness suspected to be related to fluticasone furoate.

Bias and limitations inherent to the PMS study design were seen in this study. Limitation include early termination due to a mandate from the Philippine FDA to stop PMS studies by December 2012. Only 439 out of the intended 3,000 subjects were enrolled.

Conclusion

Fluticasone furoate nasal spray, among indicated patients with AR showed AEs which approximate AE of other similar post-marketing studies with incidence of less than one percent for each event.[21,22] No SAEs nor drug-related deaths were reported throughout the duration of the study. Epistaxis, rhinalgia, rhinorrhea, hypersomnia and nasal dryness and discomfort are AEs found to be possibly related to fluticasone furoate nasal spray.

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Appendices

Appendix I. Medical history and pre-existing illness/condition by medDRA

System Organ Class	Preferred Term	Number of Patients (%*)	Number of Events
Ear and labyrinth disorders		8 (1.9)	8
	Cerumen impaction	1 (0.2)	1
	Eustachian tube dysfunction	1 (0.2)	1
	Meniere's disease	1 (0.2)	1
	Middle ear inflammation	1 (0.2)	1
	Vertigo	1 (0.2)	1
	Vertigo positional	3 (0.7)	3
Endocrine disorders		1 (0.2)	1
	Goitre	1 (0.2)	1
Eye disorders		2 (0.5)	2
	Eyelid oedema	1 (0.2)	1
	Lacrimation increased	1 (0.2)	1
Gastrointestinal disorders		2 (0.5)	2
	Ankyloglossia	1 (0.2)	1
	Aphthous stomatitis	1 (0.2)	1
Infections and infestations		111 (26.4)	118
	Acute sinusitis	7 (1.7)	7
	Acute tonsillitis	2 (0.5)	2
	Adenoiditis	1 (0.2)	1
	Appendicitis	1 (0.2)	1
	Bronchitis	1 (0.2)	1
	Cellulitis	1 (0.2)	1
	Chronic sinusitis	10 (2.4)	10
	Chronic tonsillitis	1 (0.2)	1
	Diverticulitis	1 (0.2)	1
	Ear infection fungal	1 (0.2)	1
	Laryngitis	2 (0.5)	2
	Mastoiditis	1 (0.2)	1
	Nasopharyngitis	4 (1.0)	4
	Otitis externa	3 (0.7)	3
	Otitis media	12 (2.9)	12
	Otitis media acute	5 (1.2)	5
	Otitis media chronic	5 (1.2)	5
	Pharyngitis	9 (2.1)	9
	Rhinitis	3 (0.7)	3
	Sinusitis	45 (10.7)	45
	Tonsillitis	1 (0.2)	1
	Upper respiratory tract infection	2 (0.5)	2
Metabolism and nutrition disorders		7 (1.7)	7
	Diabetes mellitus	4 (1.0)	4
	Dyslipidaemia	1 (0.2)	1
	Type 2 diabetes mellitus	2 (0.5)	2
Musculoskeletal and connective tissue disorders		4 (1.0)	4
	Scoliosis	1 (0.2)	1
	Spondylitis	1 (0.2)	1
	Temporomandibular joint syndrome	2 (0.5)	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1 (0.2)	1
	Nasopharyngeal cancer	1 (0.2)	1
Nervous system disorders		9 (2.1)	9
	Anosmia	1 (0.2)	1
	Cerebrovascular accident	2 (0.5)	2
	Dizziness	1 (0.2)	1
	Migraine	3 (0.7)	3
	Migraine without aura	1 (0.2)	1
	Neuropathy peripheral	1 (0.2)	1
Respiratory, thoracic and mediastinal disorders		42 (10.0)	57
	Adenoidal hypertrophy	1 (0.2)	1
	Allergic cough	3 (0.7)	3
	Allergic sinusitis	1 (0.2)	1
	Asthma	8 (1.9)	8

Appendix I. Medical history and pre-existing illness/condition by medDRA (continuation)

System Organ Class	Preferred Term	Number of Patients (%*)	Number of Events
	Cough	2 (0.5)	2
	Nasal congestion	3 (0.7)	3
	Nasal polyps	19 (4.5)	19
	Nasal septum deviation	5 (1.2)	5
	Reflux laryngitis	12 (2.9)	12
	Rhinorrhoea	1 (0.2)	1
	Snoring	1 (0.2)	1
	Vocal cord thickening	1 (0.2)	1
Skin and subcutaneous tissue disorders		2 (0.5)	2
	Dermatitis atopic	1 (0.2)	1
	Eczema	1 (0.2)	1
Vascular disorders		16 (3.8)	16
	Hypertension	16 (3.8)	16

**The denominator used in the computation of percentages is the safety population.*

Appendix II. Concomitant medications taken

Anatomical Group	Generic Name	Number of Patients (%*)	Number of Events
Alimentary tract and metabolism		32 (7.6)	50
	Ascorbic acid	1 (0.2)	2
	Chlorhexidine gluconate	1 (0.2)	1
	Domperidone	2 (0.5)	2
	Esomeprazole	2 (0.5)	3
	Gliclazide	1 (0.2)	2
	Lansoprazole	1 (0.2)	2
	Metformin	3 (0.7)	4
	Metformin hydrochloride	1 (0.2)	1
	Omeprazole	8 (1.9)	12
	Pantoprazole	2 (0.5)	2
	Pantoprazole + domperidone	1 (0.2)	2
	Pantoprazole sodium sesquihydrate	1 (0.2)	1
	Rabeprazole	3 (0.7)	3
	Rabeprazole sodium	3 (0.7)	4
	Sitagliptin phosphate	1 (0.2)	1
	Sodium chloride	1 (0.2)	2
	Vit. B nos	1 (0.2)	2
	Vitamins nos	2 (0.5)	4
Antiinfectives for systemic use		111 (26.4)	150
	Amoxicillin	2 (0.5)	2
	Amoxicillin clavulanate	1 (0.2)	1
	Amoxicillin trihydrate	42 (10.0)	55
	Azithromycin	2 (0.5)	2
	Cefaclor	1 (0.2)	1
	Cefuroxime	5 (1.2)	5
	Cefuroxime axetil	2 (0.5)	2
	Ciprofloxacin	4 (1.0)	4
	Clarithromycin	34 (8.1)	46
	Clindamycin	2 (0.5)	3
	Cloxacillin	1 (0.2)	1
	Dexamethasone + neomycin + polymyxin	1 (0.2)	1
	Fosamprenavir calcium	1 (0.2)	1
	Levofloxacin	13 (3.1)	24
	Sulbactam + ampicillin	2 (0.5)	2
Blood and blood forming organs		2 (0.5)	2
	Cilostazol	1 (0.2)	1
	Clopidogrel bisulfate	1 (0.2)	1

Appendix II. Concomitant medications taken (continuation)

Anatomical Group	Generic Name	Number of Patients (%*)	Number of Events
Cardiovascular system		17 (4.0)	29
	Amlodipine	8 (1.9)	12
	Amlodipine besilate	1 (0.2)	1
	Atenolol	1 (0.2)	2
	Diltiazem hydrochloride	1 (0.2)	1
	Irbesartan	1 (0.2)	1
	Losartan	2 (0.5)	2
	Losartan potassium	1 (0.2)	1
	Pravastatin sodium	1 (0.2)	1
	Rosuvastatin	1 (0.2)	2
	Telmisartan	2 (0.5)	4
	Valsartan + hydrochloro-thiazide	1 (0.2)	2
Dermatologicals		6 (1.4)	7
	Methylprednisolone	5 (1.2)	6
	Tolnaftate	1 (0.2)	1
Nervous system		9 (2.1)	15
	Betahistine	4 (1.0)	5
	Betahistine hydrochloride	1 (0.2)	1
	Cinnarizine	2 (0.5)	2
	Diazepam	1 (0.2)	2
	Flunarizine	2 (0.5)	3
	Orphenadrine	1 (0.2)	2
Respiratory system		193 (45.8)	375
	Acetylcysteine	4 (1.0)	4
	Ambroxol	6 (1.4)	7
	Ambroxol hydrochloride	2 (0.5)	2

Appendix III. Dosing information at baseline

	Value
Baseline total daily dose, n(%*)	
55 ug	10 (2.4)
110 ug	298 (70.8)
Others	113 (26.8)
Missing, n	0
Dosing requirement, n(%*)	
OD	265 (62.9)
BID	131 (31.1)
TID	0 (0.0)
Others	24 (5.7)
Missing, n	1
Mean	90.0
Median	110.0
Standard deviation	35.2
Minimum	10.0
Maximum	120.0

** The denominator used in the computation of percentages is the safety population.*