

Fluticasone Furoate (Arnuity) Ellipta

Abbreviated Review

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section.

FDA Approval Information

Description	Once daily inhaled corticosteroid
Indication(s) Under Review	Maintenance treatment of asthma as prophylactic therapy in patients ≥ 12 years of age
Dosage Form(s) Under Review	Inhalation powder containing 100mcg or 200mcg of fluticasone furoate per actuation
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <i>See Other Considerations for additional REMS information</i>
Pregnancy Rating	Category C

Background

Purpose for Review The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating fluticasone furoate for possible addition to the VA National Formulary

Other Therapeutic Options

Formulary Alternatives	Other Considerations
Mometasone DPI or MDI	The DPI is administered once daily or BID
Non-formulary Alternatives	Other Considerations
Fluticasone dipropionate	Administered BID
Flunisolide	(there are no national CFU or restrictions for these non-formulary agents)
Budesonide	
Beclomethasone	
Ciclesonide	

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline using the search fluticasone furoate. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

The efficacy review is limited to asthma trials > 12 weeks in duration using the marketed dose. The fixed-dose combination trials of fluticasone furoate/vilanterol in patients with asthma were only included if there was fluticasone furoate monotherapy arm.

General inclusion criteria: diagnosis of asthma for ≥ 12 weeks, ≥ 12 years old, pre-bronchodilator FEV1 40-90% predicted and reversibility of $\geq 12\%$ and ≥ 200 ml following albuterol

Select demographic information: the mean age across studies was 40.1-47.3; 65% were female, and the mean duration of asthma across studies was 15.5-20.8yrs.

Primary outcome for the 24 week trials was pre-dose FEV1. For Bateman et al, the primary outcome was severe exacerbations. The trials by Lotvall and O'Byrne also included percentage of rescue-free 24-hour periods as a powered secondary outcome. Other secondary outcomes included morning and evening peak flow, quality of life, asthma control.

Trough FEV1 and Rescue-Free 24hr Periods

The improvement in trough FEV1 and rescue-free 24 hour period was significantly greater with both FF 100 QD and FP 250 than placebo. There was numerically greater improvement in the above outcomes with FF200 versus FF100. Trials comparing FF alone to FF/VI showed significantly greater improvement with the combination.

Table 1: Trough FEV1 and Rescue-Free 24 Hour Periods

Study	Treatment Arms	n	Baseline FEV1 % predicted/FEV1 (L)	Δ trough FEV1 (mL)	Baseline rescue-free 24-h periods (%)	Δ rescue-free 24-h periods (%)
Lotvall 24-weeks R, DB, DD	FF 100 QD	114		161*	13.3	14.8*
	FP 250 BID	114	72.5/2.35	159*	17.1	17.9*
	PBO	115		15	18.5	Diff vs. PBO
Woodcock 24-weeks R, DB	FF100 QD	119		208	14.3	21.3
	FF200 QD	119	68.1/2.06	284	11.5	23.1
O'Byrne 24-weeks R, DB, DD	FF200 QD	194		201	7.8	26.6
	FP500 BID	195	66.9/2.15	183	6.3	31.9
	FF/VI 200/25 QD	197		394 [^]	7.6	38.2 [‡]
Bateman ≥24-78 weeks R, DB	FF100 QD	1010		Tx diff (FF/VI – FF) 89 [‡]	NA	NA
	FF/VI 100/25 QD	1009	68.9/2.11			

Abbreviations: DB=double-blind; DD=double dummy; FF=fluticasone furoate; FP=fluticasone propionate; NA=not applicable; PBO=placebo; R=randomized; VI=vilanterol

*Significant vs. placebo

[^]FF/VI significant vs. FF and FP

[‡]FF/VI significant vs. FF

Asthma Quality of Life Questionnaire and Asthma Control

All active treatments improved quality of life and asthma control. There were no significant differences (where measured) between groups. Compared to placebo, both active treatments had significantly greater improvement than placebo.

Severe Asthma Exacerbations

Severe asthma exacerbation was defined as deterioration of asthma requiring use of systemic corticosteroids for ≥3 days, or inpatient hospitalization, or emergency department visit due to asthma requiring systemic corticosteroids. It was a primary outcome in Bateman et al. Events were adjudicated by a committee. In the other 3 trials, severe exacerbation data were collected as part of the routine adverse event analysis.

In Bateman et al., patients were required to have had ≥ 1 asthma exacerbation requiring systemic corticosteroids and/or hospitalization or emergency room visit in the previous year. In the year prior to the study, 57% had 1 exacerbation, 24% had 2 exacerbations, 10% had 3 exacerbations, and 9% had ≥ 4 exacerbations.

The probability of a severe asthma exacerbation by 52 weeks was 15.9% for FF and 12.8% for FF/VI. The hazard ratio was 0.79 [95%CI 0.64, 0.98]; p=0.036 favoring FF/VI. The rate of severe exacerbations per patient-year was 0.19 and 0.14 respectively. The percentage of patients experiencing ≥ 1 severe exacerbation was 18% and 15% respectively. The mean duration of the exacerbation was 11 days in both groups.

The exacerbation rates for the remaining trials are shown in **Table 2**.

Table 2: Severe Asthma Exacerbations (24-Week Trials)

	Lotvall			Woodcock		O'Byrne		FF/VI 200/25 QD
	FF100 QD	FP250 BID	PBO	FF100 QD	FF200 QD	FF200 QD	FP500 BID	
Severe exacerbation n (%)	3 (3)	2 (2)	8 (7)	14 (13)	13 (12)	6 (3)	2 (1)	0

Potential Off-Label Use

Use in COPD

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	None
Contraindications	Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures Severe hypersensitivity to milk proteins or any ingredients of FF
Warnings/ Precautions	The warnings and precautions for FF are the same as those listed for other inhaled corticosteroids. There were no warnings and precautions listed unique to FF
Safety Considerations	The safety program for FF includes 10 clinical trials (n=6219) ranging from 8-76 weeks duration and doses ranging from 25-800mcg. The marketed doses of 100mcg and 200mcg were evaluated in 1663 and 608 patients respectively.

Oral candidiasis

The number of patients with oral candidiasis varied from study to study with no specific pattern.

Table 3: Oral Candidiasis

	Lotvall			Woodcock			O'Byrne		Bateman	
	FF100	FP250	PBO	FF100	FF200	FF200	FP500	FF/VI 200/25	FF100	FF/VI 100/25
Oral candidiasis (n)	6	2	0	1	5	1	2	5	NR	NR

NR=not reported

Adverse Reactions

Common adverse reactions

Table 4: Most Common On-treatment AEs (%)

	Lotvall			Woodcock			O'Byrne		Bateman	
	FF100	FP250	PBO	FF100	FF200	FF200	FP500	FF/VI 200/25	FF100	FF/VI 100/25
Headache	6	6	4	10	13	7	8	6	18	19
Nasopharyngitis	8	4	5	12	13	14	20	13	13	15
URI	6	5	5	2	6				9	7
Bronchitis	7	4	6	12	7	3	3	4	7	6
Cough	-	-	-	-	-	3	7	2	6	5
Oropharyngeal pain	-	-	-	-	-	4	4	2	5	4
Influenza				4	7	4	4	3	4	5
Pharyngitis	-	-	-	6	3	1	3	2	-	-
Sinusitis	-	-	7	4	4	2	2	-	-	-

Death/Serious adverse reactions (SAE)

There were no deaths in the three 24-week trials. In the long-term trial, there were 2 deaths in the FF group and 1 death in the FF/VI group. None were considered treatment-related. The frequency of on-treatment SAEs is shown in **Table 5**. In Lotvall and Woodcock, none of the events were considered to be treatment-related. In O'Byrne, 2 events were deemed treatment-related; 1 in the FF/VI group (atrial fibrillation) and 1 in the FP500 group (hemoptysis). In Bateman, four on-treatment or post-treatment SAEs were considered to be treatment-related; three events in FF group (pleurisy, asthma, non-cardiac chest pain) and one in the FF/VI group (tachycardia).

Table 5: On-Treatment SAE (%)

Lotvall			Woodcock			O'Byrne		Bateman	
FF100	FP250	PBO	FF100	FF200	FF200	FP500	FF/VI 200/25	FF100	FF/VI 100/25
4	<1	2	3	3	<1	1	3	3	4

FF and FF/VI dosed once daily; FP dosed BID

Discontinuations due to adverse reactions Data from safety program: 2% for both doses of FF; ≤1% for placebo

Drug Interactions

Drug-drug interactions	FF is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases systemic exposure to FF. Use caution when considering the coadministration of FF with long term ketoconazole and other known strong CYP3A4 inhibitors.
Drug-food interactions	None
Drug-lab interactions	None

Risk Evaluation

As of insert date June 2015

Sentinel event advisories	None Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First Databank	ISMP	Clinical Judgment
Fluticasone furoate	None	None	None	Fluticasone propionate Flunisolide Fludrocortisone
Arnuity Ellipta	None	None	None	Breo Ellipta Incruse Ellipta

Other Considerations**Storage**

Store at room temperature between 68° and 77°F (20° and 25°C); excursions from 59°F to 86°F (15° to 30°) are permitted. Store inside the unopened moisture-protective foil tray and only remove from the tray immediately before initial use. Discard FF 6 weeks after opening foil tray or when the counter reads "0" whichever comes first.

Dosing and Administration

- One inhalation once daily by the oral inhaled route
- Do not use FF more than one time every 24 hours
- Usual starting dose for patients not on an ICS is 100mcg. For other patients, dose should be based on previous asthma drug therapy and disease severity. For those not responding to 100mcg once daily, the dose may be increased to 200mcg once daily

Projected Place in Therapy

Fluticasone furoate is an option for patients who have difficulty adhering to twice daily inhaled steroids. The formulary agent mometasone (dry powder inhaler) can also be administered once daily if the dose is ≤ 200mcg daily; higher doses are administered twice daily.

References

Lötvall J, Bleecker ER, Busse WW, et al. Efficacy and safety of fluticasone furoate 100 µg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomized trial. *Respir Med*. 2014; 108(1):41-9.

Woodcock A, Lötvall J, Busse WW, et al. Efficacy and safety of fluticasone furoate 100 µg and 200 µg once daily in the treatment of moderate-severe asthma in adults and adolescents: a 24-week randomized study. *BMC Pulm Med*. 2014;14:113. doi: 10.1186/1471-2466-14-113.

O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *Eur Respir J*. 2014;43(3):773-82.

Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. *Thorax* 2014;69(4):312-9.

Product Package Insert for Fluticasone Furoate (Arnuity) Ellipta

**Prepared by Deb Khachikian, PharmD
July 2015**