CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205625Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Risk Management Review

Date:	March 19, 2014
Reviewer(s):	Kendra Worthy, Pharm. D., Division of Risk Management (DRISK)
Team Leader	Reema Mehta, Pharm. D., M.P.H., DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	TBD-Ellipta (fluticasone furoate)
Therapeutic Class:	Corticosteroid
Dosage form:	Dry Powder Inhaler (DPI)
Application Type/Number:	NDA 205625
Applicant/sponsor:	GlaxoSmithKline (GSK)
OSE RCM #:	2013-2537; 2013-2521

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the need for a Risk Evaluation and Mitigation Strategy (REMS) for TBD-Ellipta (fluticasone fuorate) dry powder inhaler (DPI), NDA 205625, received from GlaxoSmithKline (GSK) on October 22, 2013.

The application was initially filed as a new molecular entity (NME) but was later reclassified as a 505(b)(1) for a non-NME[1].

2 BACKGROUND

Fluticasone furoate (FF) is a corticosteroid administered by oral inhalation at a dose of 100 mcg or 200 mcg once daily. The proposed indication is for once daily maintenance treatment of asthma in patients 12 years of age and older.

FF was approved in 2007 as Veramyst nasal steroid for seasonal and perennial allergic rhinitis in adults and children aged two years and older (NDA22-051) as well as a combination product as Vilanterol (Breo Ellipta, NDA 204275) for maintenance treatment of COPD and reduction of exacerbation in 2013.

GSK submitted the original NDA for Breo Ellipta with a proposed REMS consisting of a Medication Guide, communication plan, and timetable for submission of assessments consistent with the REMS that was required for the entire LABA class for the risk of asthma-related deaths, intubations, and hospitalizations associated with the use of LABAs. DRISK reviewed the application and determined that and the risks associated with Breo Ellipta could be adequately managed through labeling and routine pharmacovigilance; in addition, the Agency internally agreed in June 2012 that the REMS for LABAs were no longer required[2].

(b) (4)

sponsor did not submit a proposed REMS for TBD-Ellipta.

3 MATERIALS REVIEWED

- Email communications from Tracy Kruzick, Medical Officer and Prasad Peri, CMC, dated January 9, 2014.
- Medical Officer Filing Review dated December 19, 2013, Tracy Kruzick, Medical Officer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).
- Regulatory Project Manager Filing Review dated December 16, 2013, Phuong Ton, DPARP.

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[1] Email communications from Tracy Kruzick, Medical Officer and Prasad Peri, CMC, dated January 9, 2014.

[2] DRISK REMS review of Breo Ellipta dated April 22, 2013, Yasmin Choudhry, Medical Officer.

- GSK's Proposed Risk Management Plan, submitted October 22, 2013.
- DRISK REMS review of Breo Ellipta dated April 22, 2013, Yasmin Choudhry, Medical Officer.
- Approval Letters for Veramyst (April 27, 2007) and Breo Ellipta (May 10, 2013), Drugs@FDA.

4 OVERVIEW OF CLINICAL PROGRAM

Table 5. Pivotal Phase 3 Study Results

Study	Design	Treatment	LS mean change	Change from baseline in trough FEV1
FFA112059	MC, R, DB, DD, P, AC	FF 100 QD FP 250 BID Placebo	161 ml 159 ml 15 ml	146 mL [36,257] p = .009
HZA106827	MC, S, R, DB, PG, PC	FF 100 QD FF/VI 100/25 QD Placebo	332 ml 368 mL 196 ml	136 mL [51,222] p = 0.002
FFA114496	R, DB, PG	FF 100 QD FF 200 QD	208 ml 284 ml	77 mL [-39,192]
HZA106829 Non-inferiority	MC, R, DB, PG, AC	FF 200 QD FP 500 BID	201 mL 183 mL	18 mL [-66,102]

Table from Medical Officer Filing Review, p.6, dated December 19, 2013, Tracy Kruzick, Medical Officer, DPARP.

The DPARP medical officer noted that the sponsor provided four studies in support for the efficacy of TBD Ellipta (listed in Table 5 above) and seven studies for safety. The sponsor reports:

- statistical superiority of the 100 mcg dose over placebo when evaluating the primary endpoint of change from baseline in trough FEV1 (146 mL, p=0.009 in study FFA112059 and 136 mL, p=0.002 in HZA106827); and
- numerical (not statistically significant) improvement of the 200 mcg dose over the 100 mcg dose[3].

4.1 SAFETY CONCERNS

Within the pooled safety database, a total of 3218 patients have received doses of FF across the entire program. There were two deaths in the 100 mcg populations; one due to respiratory failure from carcinoma 173 days after initiation of FF therapy; the other due to pneumonia 114 days after starting treatment with FF. The most common serious adverse events were asthma and pneumonia, which occurred in less than 1% of subjects.

[3] Medical Officer Filing Review, dated December 19, 2013, Tracy Kruzick, Medical Officer, DPARP.

The most commonly reported adverse events in the clinical trials were headache, nasopharyngitis, upper respiratory tract infection, and bronchitis[3].

5 RISK MANAGEMENT PROPOSED BY APPLICANT

The Sponsor submitted a proposed (b) (4) risk management plan with this application that includes the potential risks outlined below.

- Growth retardation in children
- (b) (4)
- Hypersensitivity
- Adrenal Suppression
- Ocular Disorders
- (b) (4)

The most common adverse event from the Sponsor-reported potential risks was dose-related local steroid effects; the overall incidence was less than 1% for both treatment groups. The sponsor proposed to manage these risks with professional labeling (Warnings and precautions Section) (b) (4) For hypersensitivity, GSK proposed a contraindication in the professional labeling. The Sponsor also stated that (b) (4). Summary safety data for these risks is outlined in the table below .

Table 12. Summary of AE of special interest in the pooled safety database:

Special Interest AE (Preferred Term)	Number (%) of subjects			
	Placebo N=858	FF 50 N=338	FF 100 N=1663	FF 200 N=608
Local steroid effects	15 (2)	7 (2)	122 (7)	48 (8)
Oropharyngeal pain	11 (1)	2 (<1)	71 (4)	19 (3)
Dysphonia	4 (<1)	1 (<1)	23 (1)	11 (2)
Oral candidiasis	0	4 (1)	18 (1)	8 (1)
Oropharyngeal candidiasis	1 (<1)	1 (<1)	7 (<1)	9 (1)
LRTI excluding pneumonia	16 (2)	1 (<1)	114 (7)	19 (3)
Bronchitis	15 (2)	0	98 (6)	15 (2)
Hypersensitivity	13 (2)	3 (<1)	41 (2)	6 (<1)
Bone disorders	0	2 (<1)	21 (1)	2 (<1)
Pneumonia	2 (<1)	0	10 (<1)	4 (<1)
Effects on glucose	0	0	11 (<1)	2 (<1)
Ocular effects	0	0	6 (<1)	0

Source: Summary of clinical safety table 20

Table from Medical Officer Filing Review, p.9, dated December 19, 2013, Tracy Kruzick, Medical Officer, DPARP.

[4] GSK's Proposed Risk Management Plan, submitted October 22, 2013.

[5] Medical Officer Filing Review, dated December 19, 2013, Tracy Kruzick, Medical Officer, DPARP.

6 DISCUSSION

The proposed (b) (4) Risk Management Plan for FF is acceptable to manage the potential risks outlined by the sponsor. DRISK previously concluded that the combination product FF/Vilanterol (Breo Ellipta) did not require a REMS[6]. The safety profile of the single ingredient FF preliminarily appears consistent with the known safety profile for Breo Ellipta and Veramyst.

7 CONCLUSION AND RECOMMENDATIONS

In conclusion, at this time, risk mitigation measures beyond professional labeling are not warranted for TBD Ellipta. The safety profile for TBD Ellipta is consistent with the known safety profile for comparable approved products. The benefit-risk profile for TBD Ellipta seems favorable and the risks can be mitigated through professional labeling.

Should the Division have any concerns or questions, or feel that a REMS may be warranted for this product, please contact DRISK.

[6] DRISK REMS review of Breo Ellipta dated April 22, 2013, Yasmin Choudhry, Medical Officer.

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/s/

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03/19/2014

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