CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202236Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA/Supporting document no.	202-236
Submission Date	04/01/11
Brand Name	TBD
Generic Name	Azelastine 0.1% and Fluticasone 0.037%
Reviewer	Lokesh Jain, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Meda Pharmaceuticals
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	Nasal spray
Indication	Relief of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older
Dosage Regimen	• age 12 years and older: 1 spray per nostril BID (total azelastine dose of 548 µg/day and total fluticasone dose of 200 mcg/day) • not indicated in age group < 12 years

1. Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology finds NDA 202236 acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Meda pharmaceutical, Inc. has submitted NDA #202236 seeking marketing approval for a fixed dose combination product containing azelastine hydrochloride (AZE; 0.1% w/w) and fluticasone propionate (FLU; 0.0365% w/w), presented as a nasal spray formulation MP29-02. If approved it will be the first fixed dose combination nasal spray product to be marketed in the USA.

MP29-02 is intended for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. The monotherapy components AZE and FLU were approved under NDA 20-114 and NDA 20-121, respectively, for symptoms of seasonal allergic rhinitis (SAR), vasomotor rhinitis (VMR), and perennial allergic rhinitis (PAR).

In support of this NDA, sponsor conducted five clinical efficacy and safety studies and two clinical pharmacology single-dose relative bioavailability studies. The objective of clinical pharmacology studies was to assess the relative bioavailability of AZE and FLU from MP29-02 against monotherapy products to identify any potential drug-drug

interaction (DDI) and formulation issues. Key results from clinical pharmacology studies are listed below:

- Co-administration of FLU and AZE does not affect systemic exposures of each other
- Systemic exposure of AZE from MP29-02 was within ±20% of the exposure from Astelin®, a FDA approved commercially available AZE product
- Systemic exposure of FLU from MP29-02 is 44-61% higher than the exposure from a FDA approved commercially available FLU generic product
- Higher systemic exposures of FLU from MP29-02 fall in the range of exposures for which no significant effect on HPA-axis function has been identified

Dosing information for intrinsic and extrinsic factors was bridged from that of the individual components.

2. Question Based Review

2.1 What are the highlights of the formulations of the drug product?

The formulations used in clinical pharmacology studies were as follows:

1. investigational AZE-FLU combination product: **MP29-02**
2. investigational monotherapy products
    a. a formulation and packaging similar to MP29-02, except the absence of AZE (i.e., only FLU in MP29-02 vehicle)
    b. a formulation and packaging similar to MP29-02, except the absence of FLU (i.e., only AZE in MP29-02 vehicle)
3. commercially available monotherapy products
    a. FLU generic product, marketed by Roxane Laboratories
    b. Astelin®, an AZE monotherapy product marketed by Meda pharmaceuticals

Comparison of the composition of combination vs. monotherapy investigational products is shown in Table 1.

The to be marketed combination product is same as the MP29-02 product used in Phase 3 clinical trials supporting safety and efficacy for this NDA.

Table 1: Description and composition of MP29-02 and investigational monotherapy drug products

Ingredient	Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray			Azelastine Hydrochloride 0.1% Nasal Spray			Fluticasone Propionate 0.037% Nasal Spray		
	µg/ spray[a]	mg/g	% w/w	µg/ spray[a]	mg/g	% w/w	µg/ spray[a]	mg/g	% w/w
Drug Substances:									
Azelastine Hydrochloride	137	1.00	0.100	137	1.00	0.100	---	---	---
Fluticasone Propionate USP	50	0.365	0.0365	---	---	---	50	0.365	0.0365
Excipients:									
Glycerin USP	(b) (4		(b) (4	(b) (4		(b) (4	(b) (4		(b) (4)
Microcrystalline Cellulose and Carboxymethylcellulose Sodium NF (b) (4)									
Polysorbate 80 NF									
Edetate Disodium USP									
Benzalkonium Chloride NF[b]		0.1	0.01		0.1	0.01		0.1	0.01
Phenylethyl Alcohol USP		2.5	0.25		2.5	0.25		2.5	0.25
Purified Water USP									(b) (4)
									(b) (4)

2.2 General Attributes of the Drug

2.2.1 What are the proposed mechanism of action and therapeutic indications?

AZE is a selective histamine H_1-receptor antagonist. Antihistamines are used for symptomatic treatment of various allergic diseases. Meda pharmaceuticals markets two of the currently approved Azelastine nasal spray products - Astelin® (NDA 20-114) and Astepro® (NDA 22-371). The major difference between Astepro and Astelin is that the former contains two additional excipients, sucralose and sorbitol, which are intended to mask the distinctive bitter taste associated with the azelastine drug substance. The approved indications for azelastine and the dosage are as below:

- Treatment of symptoms of SAR
  - Age ≥ 12 years: 1-2 sprays per nostril bid (maximum daily dose (MDD) = 548-1096 µg/day)
  - Age 5-12 years: 1 spray per nostril bid (MDD = 548 µg/day)
- Treatment of symptoms of nonallergic VMR
  - Age ≥ 12 years: 2 sprays per nostril bid (MDD = 1096 µg/day)

FLU is a synthetic glucocorticoid which acts as a glucocorticoid receptor agonist. It is an anti-inflammatory agent. The approved indications for fluticasone and the dosage are as below:

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