CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202236Orig1s000

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: NDA 202,236 (DYMISTA; Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.37% Nasal Spray)
Submissions dated April 1 and July 1, 2011, respectively

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Pharmacology/Toxicology Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: December 7, 2011

I concur with the conclusions and recommendations of Dr. Marcie Wood's Review dated September 23, 2011. The review recommended approval of the application from the nonclinical perspective.

The applicant has developed a fixed dose combination of azelastine and fluticasone propionate administered as a nasal spray for the treatment of allergic rhinitis in children and adults 12 years of age and older. This is the first combination product of an anti-histamine and corticosteroid.

The nonclinical safety program for the fixed dose combination of azelastine and fluticasone propionate administered as a nasal spray is based upon the complete toxicology programs conducted with each of the monoproducts. The applicant also conducted 14-day intranasal toxicology studies in rats and dogs and a 3-month intranasal toxicology study in rats with the combination of azelastine hydrochloride and fluticasone propionate to assess for potential additive or synergistic toxic effects of the combination. There was no evidence of additive or synergistic toxic effects of the combination with particular reference to local toxicity in the nasal cavity and sinuses. See Dr. Wood's review for further details.

Dr. Wood's Review makes recommendations for changes in the product labeling in Sections 8.1, 8.3, 10, 12.1, 13.1, and 13.2.

There are no outstanding PharmTox issues.

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/s/

TIMOTHY W ROBISON
12/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 202236
Supporting document/s:	SDN 1, SDN 4
Applicant's letter date:	SDN 1: April 1, 2011
	SDN 4: July 1, 2011
CDER stamp date:	SDN 1: April 1, 2011
	SDN 4: July 1, 2011
Product:	Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.37% Nasal Spray
Indication:	Seasonal allergic rhinitis
Applicant:	Meda Pharmaceuticals, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Marcie Wood, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D., DABT
Division Director:	Badrul Chowdhury, M.D., Ph.D.
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The applicant has developed a fixed dose combination of azelastine and fluticasone propionate administered as a nasal spray for the treatment of allergic rhinitis in children and adults 12 years of age and older.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical safety program for the fixed dose combination of azelastine and fluticasone propionate administered as a nasal spray is based upon the complete toxicology programs conducted for both individual active drugs. The nonclinical programs for the individual active drugs include single dose toxicology, subchronic toxicology, chronic toxicology, reproductive toxicology, genotoxicity, and carcinogenicity studies. The applicant conducted 14-day intranasal toxicology studies in rats and dogs and 3-month intranasal toxicology study in rats with the combination of azelastine hydrochloride and fluticasone propionate to assess for potential additive or synergistic toxic effects of the combination.

In 14-day toxicology studies, the NOAEL for both the rat and the dog was the only combination dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day). There was no difference between species sensitivity to the drug combination in the 14-day studies, but the reviewer notes that the sponsor did not evaluate a range of doses of azelastine and fluticasone in the dog to identify dose limiting toxicity and/or target organs of toxicity. TK parameters were not evaluated in the 14-day rat and dog studies.

In a 3-month intranasal toxicity study in rats, the toxicity of azelastine/fluticasone combination nasal spray was compared with the Astelin (azelastine) and fluticasone propionate marketed monoproducts. Only one dose of the azelastine/fluticasone combination (0.1% azelastine and 0.0365% fluticasone propionate; 0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day) was tested, and control (0.9% sodium chloride) and placebo (vehicle) groups were also included. Azelastine systemic exposure in the combination azelastine/fluticasone treatment group was lower than the Astelin group for males and females on Days 1 and 91. Fluticasone propionate was not detected in the plasma of the combination treatment group or the fluticasone propionate monoproduct group. Body weight was decreased in males and females in the azelastine/fluticasone (-7 and -9% for males and females, respectively) and fluticasone propionate (-6 and -15% for males and females, respectively) groups on Day 91 versus controls. Body weight gain was also decreased in males and females in the azelastine/fluticasone (-10 and -17% for males and females, respectively) and fluticasone propionate (-9 and -29% for males and females, respectively) groups (Days 1-91) versus controls. Mast cells were increased in the mesenteric lymph nodes in the azelastine/fluticasone (9/10 males and 10/10 females) and fluticasone propionate (7/10 males and 8/10 females) groups versus controls. This increase was attributed to effects of fluticasone propionate. Mast cells were also increased in the mandibular lymph nodes

of males and females in the azelastine/fluticasone group only versus control, vehicle, and monoproduct groups. The toxicological significance of this finding is uncertain.

The NOAEL was determined to be the only dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day). Increased mast cells in the mandibular lymph node in the azelastine/fluticasone combination group versus control and monoproduct groups are of uncertain toxicological relevance as they were also found at high background levels in the tracheobronchial lymph nodes of control males.

1.3 Recommendations

1.3.1 Approvability

From a PharmTox perspective, the application is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

(b) (4)

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): N/A

Generic Name: Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.37% Nasal Spray

Code Name: MP29-02

Chemical Name

Azelastine Hydrochloride: (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-,monohydrochloride

Fluticasone Propionate: S-(fluoromethyl) 6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate

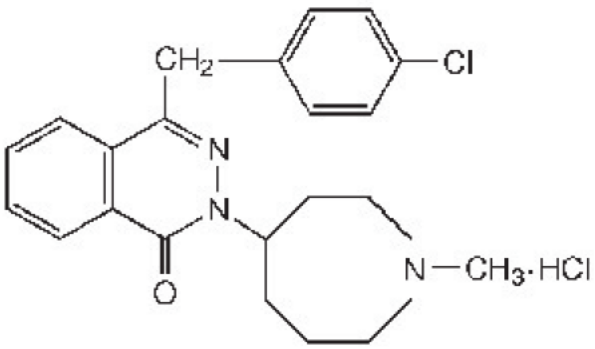
Molecular Formula/Molecular Weight

Azelastine Hydrochloride: $C_{22}H_{24}ClN_3O \bullet HCl$ / 418.37

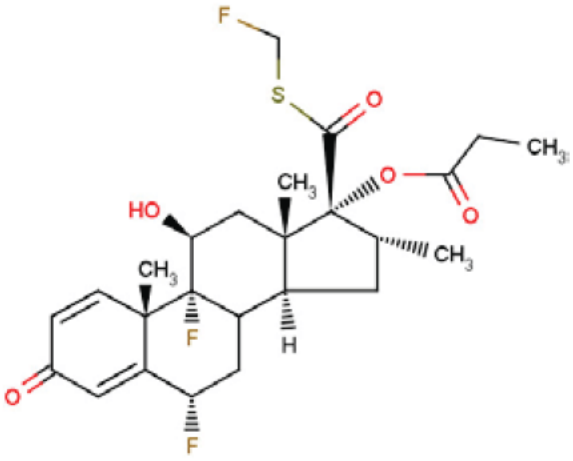
Fluticasone Propionate: $C_{25}H_{31}F_3O_5S$ / 500.6

Structure or Biochemical Description

Azelastine Hydrochloride:



Fluticasone Propionate:



Pharmacologic Class

Azelastine Hydrochloride: H_1-receptor antagonist

Fluticasone Propionate: Glucocorticoid agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 77,363 (Meda Pharmaceuticals, Inc., Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.37% Nasal Spray)
NDA 20-114 (Meda Pharmaceuticals, Inc., Astelin (Azelastine Hydrochloride) Nasal Spray)
NDA 20-121 (GlaxoSmithKline, Flonase (Fluticasone Propionate) Nasal Spray)
DMFs (b) (4)
(b) (4)
multidose nasal spray pump
actuator and cap)
DMF (b) (4) Type 1 amber glass bottles (b) (4)

2.3 Drug Formulation

The drug product contains azelastine hydrochloride and fluticasone propionate in a suspension with the following excipients.

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

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

Impurities and/or degradants will be addressed under a separate Chemistry Consultation.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication for MP29-02 is for the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. The recommended dose is one spray per nostril twice daily (137 µg of azelastine hydrochloride and 50 µg fluticasone propionate per spray) for a total daily dose of 548 µg of azelastine hydrochloride and 200 µg of fluticasone propionate.

2.7 Regulatory Background

The two active principal ingredients, azelastine and fluticasone propionate, in the proposed fixed dose combination product, are approved monoproducts. Astelin was approved on November 1, 1996 and Flonase was approved on October 19, 1994 in the US under NDA 20-114 and NDA 20-121, respectively. The recommended dose of Astelin is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 years of age (Astelin approved label, April 2007), and the recommended dose of Flonase is either two 50 µg sprays in each nostril once daily or one 50 µg spray in each nostril twice daily (starting dose in pediatric patients 4 years of age and older; Flonase approved label, March 2004).

3 Studies Submitted

3.1 Studies Reviewed

Studies reviewed under IND 77,363 for the combination of azelastine hydrochloride and fluticasone propionate include the following:

Study	Report Number	Review Location
Toxicology		
A 14-day intranasal toxicity study with 0.1% azelastine and 0.0365% fluticasone in Sprague-Dawley rats	0437RM57.006	IND 77,363
A 14-day intranasal toxicity study with 0.1% azelastine and 0.0365% fluticasone in Beagle dogs	0437DM57.007	IND 77,363
A 90-day intranasal toxicity study with azelastine and fluticasone in Sprague-Dawley rats	0470RM57.001	IND 77,363

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of IND 77,363 dated May 3, 2007
Pharmacology and Toxicology Review of IND 77,363 dated July 2, 2008
Pharmacology and Toxicology Review of IND 77,363 dated August 10, 2010
Pharmacology and Toxicology Review of IND 77,363 dated August 8, 2011
Pharmacology and Toxicology Review of NDA 20-114 (Astelin)
Pharmacology and Toxicology Review of NDA 20-121 (Flonase)

4 Pharmacology

4.1 Primary Pharmacology

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

4.2 Secondary Pharmacology

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

4.3 Safety Pharmacology

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

See NDA 20-114 and NDA 20-121 for ADME studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

5.2 Toxicokinetics

See NDA 20-114 and NDA 20-121 for TK studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

Toxicokinetic parameters of MP29-02 were assessed in a 3-month toxicology study in rats under IND 77,363.

6 General Toxicology

6.1 Single-Dose Toxicity

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

6.2 Repeat-Dose Toxicity

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

See the attached reviews of 14-day intranasal toxicology studies in rats and dogs and 3-month intranasal toxicology study in rats with the combination of azelastine hydrochloride and fluticasone propionate under IND 77,363.

7 Genetic Toxicology

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

8 Carcinogenicity

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

9 Reproductive and Developmental Toxicology

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

10 Special Toxicology Studies

See NDA 20-114 and NDA 20-121 for studies conducted with azelastine hydrochloride and fluticasone propionate, respectively.

11 Integrated Summary and Safety Evaluation

The sponsor has developed an azelastine hydrochloride + fluticasone propionate (MP29-02) combination nasal spray for the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. The recommended dose is one spray per nostril twice daily (137 µg of azelastine hydrochloride and 50 µg fluticasone propionate per spray) for a total daily dose of 548 µg of azelastine hydrochloride and 200 µg of fluticasone propionate.

The nonclinical safety program for MP29-02 is based upon the complete nonclinical safety programs conducted for both individual active drugs (NDA 20-114 for azelastine hydrochloride and NDA 20-121 for fluticasone propionate) as well as bridging toxicology studies with the combination up to 3 months in duration. The nonclinical programs for the individual active drugs, azelastine and fluticasone propionate, included pharmacology, safety pharmacology, toxicology, genotoxicity, carcinogenicity, and reproductive toxicology studies. The applicant conducted 14-day intranasal toxicology studies in rats and dogs and 3-month intranasal toxicology study in rats with the combination of azelastine hydrochloride and fluticasone propionate to assess for potential additive or synergistic toxic effects of the combination.

Pharmacology:

Azelastine hydrochloride: Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H_1-receptor antagonist activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H_1-receptor antagonist activity.

Fluticasone propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. In vitro dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25, and 0.17 nM concentrations, respectively. Fluticasone propionate was 3-fold to 5-fold more potent that dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Safety Pharmacology:

Azelastine hydrochloride: The effects of azelastine hydrochloride on the cardiovascular, behavioral, autonomic, and neurologic systems were evaluated in mice, rats, cats, and dogs.

Azelastine hydrochloride administered at high oral doses in mice and rats produced little or no apparent CNS changes except depressed motor activity in mice at doses $\geq$20 mg/kg. However, the administration of high doses (10-30 mg/kg SC) to dogs and 3-6 mg/kg IV to cynomolgus monkeys produced CNS stimulation and even convulsions at 10 mg/kg IV in monkeys.

In general, azelastine hydrochloride in therapeutic dose ranges usually effective against allergic responses was devoid of any effects on the cardiovascular and respiratory systems of anesthetized rats, dogs and cats.

Intravenous administration of azelastine hydrochloride to rats, dogs and cats did not affect systemic blood pressure or heart rate. However, higher doses (5-10 mg/kg, depending on species tested) resulted in increase or decrease in blood pressure and in heart rate.

In dogs, 1 mg/kg IV exerted long-lasting reduction of ST segment elevation. Orally, ECG changes, prolonged Q-T intervals at 20 mg/kg and prolonged QRS and QT intervals were observed at ≥40 mg/kg in one toxicity study. In addition, localized myocardial degeneration in the heart and adipose cell infiltration in the interstitial tissue of the myocardium have been noted at 40 and 60 mg/kg, respectively, suggesting an effect of azelastine administration on the heart at very high doses.

Azelastine hydrochloride caused a dose-dependent increase in tracheobronchial secretion in the mouse with an ED50 of 0.52 mg/kg, p.o. and enhanced mucolytic activity in the tracheobronchial lumen of rats (ED50 =0.33 mg/kg). It was found to decrease mucus rigidity in beagle dogs at a dose equivalent to 3 mg/kg and decreased antigen-elevated viscoelasticity of tracheal mucus in the dogs.

Oral administration of azelastine hydrochloride at 1 to 50 mg/kg did not influence gastric motility and emptying in mice, but in rats, 1 to 10 mg/kg produced a slight acceleration of gastric emptying and retardation at 50 mg/kg. It exerted little or no effect on intestinal motility or pancreatic, biliary and salivary secretions in rats.

Fluticasone propionate: Safety pharmacology endpoints were addressed in fluticasone propionate studies conducted in mice, rats, cats, dogs, and monkeys. Following oral and SC doses, no behavioral modifications were observed in rodents. In anesthetized cats, an increased in tracheal inflation pressure and vomiting was observed following an acute dose of fluticasone. No changes in heart rates were observed following a 5 mg/kg dose of fluticasone propionate by the oral or SC routes of administration. In cynomolgus monkeys, fluticasone propionate did not cause arrhythmias or alterations in blood pressure.

ADME:

Azelastine hydrochloride: The absorption of azelastine hydrochloride is very rapid in animals evidenced by short T_{max} of 1-2 hours compared to human T_{max} of 4-6 hours following a single dose. Plasma concentrations for both animals and humans show general dose proportionality up to 30 mg/kg in rats, 60 mg/kg in mice and 2-16 mg in humans.

In both laboratory animals and humans, azelastine hydrochloride is widely distributed to body tissues with a preferential uptake by the lung observed in two species studied, rat and guinea pig. In the dog, the volume of distribution of azelastine after intravenous dosing was approximately 20 times the body weight. There is clear evidence for a

placental transfer, very low levels of transfer to the brain in rodents and a high first pass effect in animals and humans.

Azelastine hydrochloride is metabolized to various metabolites (eight possible metabolic pathways), desmethylazelastine being the major metabolite of importance. Qualitatively, the metabolic fate of azelastine hydrochloride is similar in the mouse, rat, guinea pig, dog and human. However, there are quantitative inter-species differences in the major metabolites which may be partly responsible for different toxicity between rats and dogs. Azelastine hydrochloride is not an enzyme inducer when tested for antipyrine half-life. The degree of protein binding of total radioactivity was found to be 53-57% in rats. In human, the degree of protein binding was 88% for azelastine and 97% for desmethyl-azelastine.

The major route of elimination in the animals and humans was biliary excretion. In the rat, approximately 50% and 80% of the [^{14}C] azelastine hydrochloride doses following oral and intravenous administration, respectively, were eliminated in the bile. A significant portion (19%) of the biliary radioactivity was recirculated. In humans, 25 and 50% of the radioactivity was recovered in urine and feces, respectively after five days of oral administration (4 mg) and 25 and 75% after ten days. There were no signs of tissue accumulation with repeated dosing. The terminal half-lives for elimination of azelastine and its metabolite in rodents was 4-8 hours compared to 15-25 hours in dogs and 20-50 hours in human. This long half-life of the metabolite which is active pharmacologically explains the long duration of action in azelastine hydrochloride.

Fluticasone propionate: Animal PK studies showed that fluticasone propionate is absorbed after higher oral doses, and rapid first pass metabolism affects oral bioavailability. Following SC dosing, PK profiles indicate a depot-like effect with a slow release into systemic circulation. Systemic fluticasone was also measurable after a single intranasal dose of 10 µg/kg to rats. In vitro plasma protein binding ranged from 81-95% and was similar across species. In an oral and IV distribution study, fluticasone was absorbed within 0.5 hrs and distributed mainly to the GI tract. The major metabolic pathway involves hydrolysis of the fluticasone at the 17 position to yield a carboxyl derivative that is excreted in feces and urine of mice, rats, and humans. This metabolite does not have pharmacologic activity at the glucocorticoid receptor.

Following SC administration in rats, high levels of radioactivity were found in fetal lung, liver, and placenta at 1 to 6 hrs after a single maternal dose on GD 18. Radiolabeled fluticasone was also detected in the milk of lactating female rats within 2 hrs after a single dose.

Toxicology: Oral toxicity studies up to 12-months in rats and dogs and intranasal toxicity studies up to 6-months in rats and dogs have been conducted with azelastine hydrochloride. Systemic toxicity studies (oral, SC) up to 6-months in rats and dogs and inhalation (nose-only) toxicity studies up to 78-weeks in rats and 12-months in dogs have been conducted with fluticasone propionate.

Azelastine hydrochloride: In subacute and chronic oral studies in the rat (up to 12-months duration), most of the changes in hematology (elevated serum ALP, SGOT and SGPT), urinary parameters (increased urine volume and potassium), liver and kidney weight increases, and hepatocellular changes (cytoplasmic vacuolation) occurred at oral doses ≥ 30 mg/kg/day. The target organs of toxicity were liver and kidney, and drug-induced changes appeared to be reversible. However, increased kidney weight was not accompanied by changes in kidney function parameters or histopathology, and liver findings may be considered an adaptive response. In neonatal rats, slight toxicity (comparable to that seen in adult rats) was observed at oral doses of 30 mg/kg azelastine hydrochloride and no effects were observed at oral doses ≤ 5 mg/kg.

In dogs, aggression and convulsions were observed at oral doses of azelastine hydrochloride of 10 mg/kg/day and death occurred at 20 mg/kg/day. Emesis and salivation were noted at 3 mg/kg/day. Hepatic changes were not observed in dogs at ≤ 10 mg/kg following a 12-month treatment duration.

Two six-month studies were conducted with the intranasal formulation in rats (0.2, 0.4, and 0.8 mg/day) and dogs (0.84, 1.68, and 3.36 mg/day). Except for a marginal decrease in body weight gain observed in dogs at highest dose level, there were no clinical findings indicative of systemic toxicity of azelastine hydrochloride and no signs of irritation to the epithelium lining of the nasal cavity in either species. The intranasal administration of azelastine hydrochloride up to 0.8 mg/day to rats and 3.36 mg/day to dogs appeared to be safe in these studies.

Fluticasone propionate: Fluticasone propionate was shown to be a potent glucocorticoid receptor agonist, and the toxicity profile was consistent with other glucocorticoid agonists. Toxicology studies conducted for fluticasone propionate demonstrated activity against testosterone and progesterone receptors and suggest that fluticasone may cause changes in primary and secondary sexual characteristics in males and females if administered during puberty. Rats administered fluticasone propionate by inhalation had an increase in the absence of corpora lutea and an increase in white striae in the tunica of the testes. Other target organs included the heart (perivascular inflammation in mice, coronary arteritis in dogs), stomach, lungs (septal thickening), and eyes (keratitis, retinal folding, retinal detachment in rats).

Azelastine + fluticasone propionate: Toxicology studies (up to 14-days duration in rats and dogs and 3-months in rats) have been conducted with azelastine/fluticasone (MP29-02) nasal spray under IND 77,363. In 14-day studies, the NOAEL for both the rat and the dog was the only combination dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day). There was no difference between species sensitivity to the drug combination in the 14-day studies, but the reviewer notes that the sponsor did not evaluate a range of doses of azelastine and fluticasone in the dog to identify dose limiting toxicity and/or target organs of toxicity. The intranasal safety margin for the sponsor's proposed clinical dose of 0.548 mg azelastine and 0.200 mg fluticasone was 0.6 (calculated using nasal surface areas of 221 cm^2 and 180 cm^2 for the dog and

human, respectively). TK parameters were not evaluated in the 14-day rat and dog studies.

In a 3-month intranasal toxicity study in rats, the toxicity of azelastine/fluticasone combination nasal spray was compared with the Astelin (azelastine) and fluticasone propionate marketed monoproducts. Only one dose of the azelastine/fluticasone combination (0.1% azelastine and 0.0365% fluticasone propionate; 0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day) was tested, and control (0.9% sodium chloride) and placebo (vehicle) groups were also included. Azelastine systemic exposure in the combination azelastine/fluticasone treatment group was lower than the Astelin group for males and females on Days 1 and 91. Fluticasone propionate was not detected in the plasma of the combination treatment group or the fluticasone propionate monoproduct group. Body weight was decreased in males and females in the azelastine/fluticasone (-7 and -9% for males and females, respectively) and fluticasone propionate (-6 and -15% for males and females, respectively) groups on Day 91 versus controls. Body weight gain was also decreased in males and females in the azelastine/fluticasone (-10 and -17% for males and females, respectively) and fluticasone propionate (-9 and -29% for males and females, respectively) groups (Days 1-91) versus controls. Mast cells were increased in the mesenteric lymph nodes in the azelastine/fluticasone (9/10 males and 10/10 females) and fluticasone propionate (7/10 males and 8/10 females) groups versus controls. This increase was attributed to effects of fluticasone propionate. Mast cells were also increased in the mandibular lymph nodes of males and females in the azelastine/fluticasone group only versus control, vehicle, and monoproduct groups. The toxicological significance of this finding is uncertain.

The NOAEL was determined to be the only dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day). Increased mast cells in the mandibular lymph node in the azelastine/fluticasone combination group versus control and monoproduct groups are of uncertain toxicological relevance as they were also found at high background levels in the tracheobronchial lymph nodes of control males.

The safety margins for the sponsor's proposed clinical combination dose of 0.548 mg azelastine and 0.200 mg fluticasone propionate, based on intranasal dose, are 10 for both azelastine and fluticasone in the 3-month rat intranasal toxicity study.

Table 1: Safety margins for proposed clinical doses of azelastine and fluticasone

Maximum Daily Dose (mg)	Intranasal Dose (mg/cm^2)	Intranasal Safety Margin
Human: Azelastine: 0.548 mg Fluticasone: 0.200 mg	 Azelastine: 0.0030 Fluticasone: 0.0011	 - -
Rat 3-month toxicity study: Azelastine: 0.4 mg Fluticasone: 0.146 mg	 Azelastine: 0.031 Fluticasone: 0.011	 Azelastine: 10 Fluticasone: 10

Rat and human nasal surface areas used to calculate intranasal doses were 13 cm^2 and 180 cm^2, respectively.

Genetic toxicology:

Azelastine hydrochloride: Azelastine hydrochloride was not mutagenic or clastogenic in the Ames test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test, or chromosomal aberration test in rat bone marrow.

Fluticasone propionate: Fluticasone propionate was not mutagenic in prokaryotic or eukaryotic cells in vitro, and no significant clastogenic effects were seen in cultured human peripheral lymphocytes in vitro in the mouse micronucleus test.

Carcinogenicity:

Azelastine hydrochloride**:** In 2 year carcinogenicity studies in rats and mice, azelastine hydrochloride did not show evidence of carcinogenicity at oral doses up to 30 mg/kg and 25 mg/kg, respectively.

Fluticasone propionate**:** Fluticasone propionate was not tumorigenic in mice at oral doses up to 1000 mcg/kg for 78 weeks or in rats at inhalation doses up to 57 mcg/kg for 104 weeks.

Reproductive toxicology:

Azelastine hydrochloride**:** No effects on male or female fertility were observed in rats at oral doses up to 30 mg/kg. At 68.6 mg/kg, estrous cycle duration was increased and copulatory activity and the number of pregnancies were decreased. Number of corpora lutea and implantations were decreased, but pre-implantation loss was not affected.

In mice, treatment with an oral dose of 68.6 mg/kg caused embryofetal death, malformations (cleft palate, short or absent tail, and fused, absent, or branched ribs), delayed ossification, and decreased fetal weight. No fetal or maternal effects were observed at 3 mg/kg.

In rats, treatment with an oral dose of 30 mg/kg caused malformations (oligo- and brachydactylia), delayed ossification, and skeletal variations in the absence of maternal toxicity. Treatment with an oral dose of 68.6 also caused embryofetal death and decreased fetal weight in the presence of maternal toxicity. No fetal or maternal effects were observed at 3 mg/kg.

In rabbits, treatment with oral doses of 30 mg/kg and greater caused abortion, delayed ossification, and decreased fetal weight in the presence of severe maternal toxicity. No fetal or maternal effects were observed at 0.3 mg/kg.

Fluticasone propionate**:** No effects on male or female fertility were observed in rats at SC doses up to 50 mcg/kg. Prostate weight was significantly decreased at a SC dose of 50 mcg/kg.

In mice and rats at 45 and 100 mcg/kg, respectively, fetal toxicity characteristic of potent corticosteroid compounds included embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In rabbits, treatment with a SC dose of 4 mcg/kg caused fetal weight reduction and cleft palate; however, treatment with oral doses up to 300 mcg/kg did not cause teratogenic effects (no fluticasone propionate was detected in the plasma following oral administration in this study).

Fluticasone propionate crossed the placenta following oral administration of 100 and 300 mcg/kg to rats and rabbits, respectively.

Recommendations:

The nonclinical safety program for the fixed dose combination of azelastine and fluticasone propionate nasal spray is complete.

From a PharmTox perspective, the application is recommended for approval.

There is no need for any further nonclinical studies.

Labeling Review:

8. Use in specific populations

8.1 Pregnancy

Sponsor's Proposed Labeling:

(b) (4)

(b) (4)

Recommended Labeling:

DYMISTA: Teratogenic Effects: Pregnancy Category C
There are no adequate and well-controlled studies of DYMISTA, azelastine hydrochloride only, or fluticasone propionate only in pregnant women. Animal reproduction studies of azelastine hydrochloride and fluticasone propionate in mice, rats, and/or rabbits revealed evidence of teratogenicity as well as other developmental toxic effects. Because animal reproduction studies are not always predictive of human

response, DYMISTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Azelastine hydrochloride: Teratogenic Effects: In mice, azelastine hydrochloride caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification, and decreased fetal weight at an oral dose approximately 610 times the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mg/m^2 basis at a maternal dose of 68.6 mg/kg). This dose also caused maternal toxicity as evidenced by decreased body weight. Neither fetal nor maternal effects occurred at a dose that was approximately 26 times the MRHDID (on a mg/m^2 basis at a maternal dose of 3 mg/kg).

In rats, azelastine hydrochloride caused malformations (oligo- and brachydactylia), delayed ossification and skeletal variations, in the absence of maternal toxicity, at an oral dose approximately 530 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 30 mg/kg). At a dose approximately 1200 times the MRHDID (on a mg/m^2 basis at a maternal dose of 68.6 mg/kg), azelastine hydrochloride also caused embryo-fetal death and decreased fetal weight; however, this dose caused severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose approximately 53 times the MRHDID (on a mg/m^2 basis at a maternal dose of 3 mg/kg).

In rabbits, azelastine hydrochloride caused abortion, delayed ossification and decreased fetal weight at oral doses approximately 1100 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 30 mg/kg); however, these doses also resulted in severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose approximately 11 times the MRHDID (on a mg/m^2 basis at a maternal dose of 0.3 mg/kg).

Fluticasone propionate: Teratogenic Effects: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Subcutaneous studies in the mouse and rat at doses approximately equivalent to and 4 times, respectively, the MRHDID in adults (on a mg/m^2 basis at maternal doses of 45 and 100 mcg/kg, respectively), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose less than the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 4 mcg/kg). However, no teratogenic effects were reported at oral doses up to approximately 25 times the MRHDID in adults (on a mcg/m^2 basis at a maternal dose of 300 mcg/kg) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration [*see Clinical Pharmacology (12.3)*]

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic

effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects: Fluticasone propionate crossed the placenta following oral administration of approximately 4 and 25 times the MRHDID in adults (on a mg/m^2 basis at maternal doses of 100 mcg/kg and 300 mcg/kg to rats and rabbits, respectively).

Rationale for Changes: Language was added upfront to emphasize that reproductive toxicity studies have not been conducted with the azelastine hydrochloride + fluticasone propionate combination product. Bold headings were added to highlight the results of studies conducted with each monoproduct. Finally, dose ratios were also corrected for azelastine hydrochloride, (b) (4)

8.3 Nursing Mothers

Sponsor's Proposed Labeling:

(b) (4)

Recommended Labeling:

DYMISTA: It is not known whether DYMISTA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DYMISTA is administered to a nursing woman.

Since there are no data from well-controlled human studies on the use of DYMISTA on nursing mothers, based on data for the individual components, a decision should be made whether to discontinue nursing or to discontinue DYMISTA, taking into account the importance of DYMISTA to the mother.

Azelastine hydrochloride: It is not known if azelastine hydrochloride is excreted in human milk.

Fluticasone propionate: It is not known if fluticasone propionate is excreted in human milk. However, other corticosteroids are excreted in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg of titrated fluticasone propionate (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in the milk.

Rationale for Changes: No studies were conducted with the combination to assess potential excretion into human milk.

10. Overdosage

Sponsor's Proposed Labeling:

(b) (4)

Recommended Labeling:

DYMISTA: DYMISTA contains both azelastine hydrochloride and fluticasone propionate; therefore, the risks associated with overdosage for the individual components described below apply to DYMISTA.

Azelastine hydrochloride: There have been no reported overdosages with azelastine hydrochloride. Acute azelastine hydrochloride overdosage by adults with this dosage form is unlikely to result in clinically significant adverse events, other than increased somnolence, since one (1) 23 g bottle of DYMISTA contains approximately 23 mg of azelastine hydrochloride. Clinical trials in adults with single doses of the oral formulation of azelastine hydrochloride (up to 16 mg) have not resulted in increased incidence of serious adverse events. General supportive measures should be employed if overdosage occurs. There is no known antidote to DYMISTA. Oral ingestion of antihistamines has the potential to cause serious adverse effects in children. Accordingly, DYMISTA should be kept out of the reach of children. (b) (4)

Fluticasone Propionate: Chronic fluticasone propionate overdosage may result in signs/symptoms of hypercorticism [*see Warnings and Precautions (5.2)*]. Intranasal administration of 2 mg (10 times the recommended dose) of fluticasone propionate twice daily for 7 days to healthy human volunteers was well tolerated. Single oral fluticasone propionate doses up to 16 mg have been studies in human volunteers with no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Acute overdosage with this dosage form is unlikely since one (1) 23 gram bottle of DYMISTA contains approximately 8.5 mg of fluticasone propionate.

(b) (4)

Rationale for Changes: As there is extensive clinical experience with azelastine hydrochloride and fluticasone propionate, (b) (4)

12. Clinical Pharmacology

12.1 Mechanism of Action

Sponsor's Proposed Labeling:

(b) (4)

Recommended Labeling:

DYMISTA: DYMISTA contains both azelastine hydrochloride and fluticasone propionate; therefore, the mechanisms of actions described below for the individual components apply to DYMISTA. These drugs represent two different classes of medications (a histamine H_1-receptor antagonist and a synthetic corticosteroid).

Azelastine hydrochloride: Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H_1-receptor antagonist activity in isolated tissues, animal models, and humans. Azelastine hydrochloride in DYMISTA is administered as a racemic mixture with no difference in pharmacologic activity noted between the enantiomers in in vitro studies. The major metabolite, desmethylazelastine, also possesses H_1-receptor antagonist activity.

Fluticasone propionate: Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. In vitro dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25, and 0.17 nM concentrations, respectively. Fluticasone propionate was 3-fold to 5-fold more potent that dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Rationale for Changes: Language was added upfront to emphasize that DYMISTA is a combination of both azelastine and fluticasone. Bold headings were added to highlight the class and mechanism of action of each of the monoproducts.

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's Proposed Labeling:

(b) (4)

Recommended Labeling:

DYMISTA: No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with DYMISTA; however, studies are available for the individual components, azelastine hydrochloride and fluticasone propionate, as described below.

Azelastine hydrochloride: In 2-year carcinogenicity studies in rats and mice, azelastine hydrochloride did not show evidence of carcinogenicity at oral doses up to 30 mg/kg and 25 mg/kg, respectively. These doses were approximately 530 and 220 times the maximum recommended human daily intranasal dose [MRHDID] on a mg/m^2 basis.

Azelastine hydrochloride showed no genotoxic effects in the Ames test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test, or chromosomal aberration test in rat bone marrow.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses up to 30 mg/kg (approximately 530 times the MRHDID in adults on a mg/m^2 basis). At 68.6 mg/kg (approximately 1200 times the MRHDID on a mg/m^2 basis), the duration of estrous cycles was prolonged and copulatory activity and the number of pregnancies were decreased. The numbers of corpora lutea and implantations were decreased; however, pre-implantation loss was not increased.

Fluticasone propionate: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 20 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the MRHDID in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Rationale for Changes: Language was added upfront to clarify that carcinogenicity, mutagenicity, and impairment of fertility studies have not been conducted with the azelastine hydrochloride + fluticasone propionate combination product. Bold headings were added to highlight the results of studies conducted with each monoproduct. Finally, dose ratios were also corrected for azelastine hydrochloride, (b) (4)

(b) (4)

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Table 2: Azelastine hydrochloride animal to human exposure ratios based on mg/m^2 comparisons

Drug: **Dymista: Azelastine hydrochloride**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Adult	>12	0.137	4	0.548	60	0.0091	37	0.34

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	oral	25	3	75	221.94	N/A	220	N/A
rat	oral	30	6	180	532.65	N/A	530	N/A
Reproduction and Fertility:								
rat	oral	68.6	6	411.6	1217.99	N/A	1200	N/A
rat	oral	30	6	180	532.65	N/A	530	N/A
Teratogenicity:								
mouse	oral	68.6	3	205.8	609.00	N/A	610	N/A
mouse	oral	3	3	9	26.63	N/A	26	N/A
rat	oral	68.6	6	411.6	1217.99	N/A	1200	N/A
rat	oral	30	6	180	532.65	N/A	530	N/A
rat	oral	3	6	18	53.26	N/A	53	N/A
rabbit	oral	30	12	360	1065.30	N/A	1100	N/A
rabbit	oral	0.3	12	3.6	10.65	N/A	11	N/A

Conversion, Correction, and Rounding Factors:

Human Age (yr)	Weight (kg)	Factor (kg/m²)	Species	Factor (kg/m²)	Exposure greater than x-times human	Round to nearest
0	3	25	dog	20	1	1
1	10	25	guinea pig	8	10	5
2	12	25	hamster	4	100	10
4	16	25	monkey	12	1000	100
6	20	25	mouse	3	10000	1000
12	60	37	rabbit	12		
			rat	6		

Table 3: Fluticasone propionate human exposure ratios based on mg/m^2 comparisons

Drug: **Dymista: Fluticasone Propionate**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Adult	>12	0.05	4	0.2	60	0.0033	37	0.12

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	oral	1	3	3	24.32	N/A	24	N/A
rat	inhalation	0.057	6	0.342	2.77	N/A	3	N/A
Reproduction and Fertility:								
rat	SC	0.05	6	0.3	2.43	N/A	2	N/A
Teratogenicity:								
mouse	SC	0.045	3	0.135	1.09	N/A	1	N/A
rat	SC	0.1	6	0.6	4.86	N/A	5	N/A
rat	oral	0.1	6	0.6	4.86	N/A	5	N/A
rabbit	SC	0.004	12	0.048	0.39	N/A	0.39	N/A
rabbit	oral	0.3	12	3.6	29.19	N/A	30	N/A

Conversion, Correction, and Rounding Factors:

Human Age (yr)	Weight (kg)	Factor (kg/m²)	Species	Factor (kg/m²)	Exposure greater than x-times human	Round to nearest
0	3	25	dog	20	1	1
1	10	25	guinea pig	8	10	5
2	12	25	hamster	4	100	10
4	16	25	monkey	12	1000	100
6	20	25	mouse	3	10000	1000
12	50	37	rabbit	12		
			rat	6		

12 Appendix/Attachments

Appendix 1: Pharmacology and Toxicology Review of IND 77,363 dated May 3, 2007
Appendix 2: Pharmacology and Toxicology Review of IND 77,363 dated July 2, 2008
Appendix 3: Pharmacology and Toxicology Review of IND 77,363 dated August 10, 2010
Appendix 4: Pharmacology and Toxicology Review of IND 77,363 dated August 8, 2011

APPENDIX 1

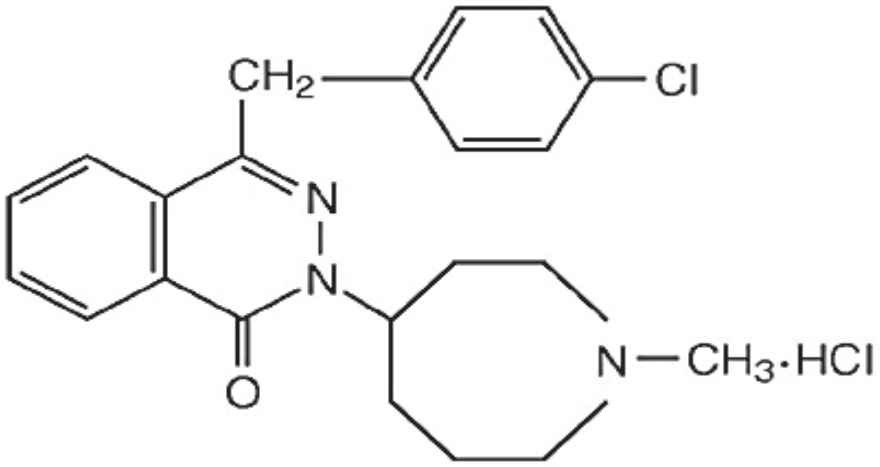
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

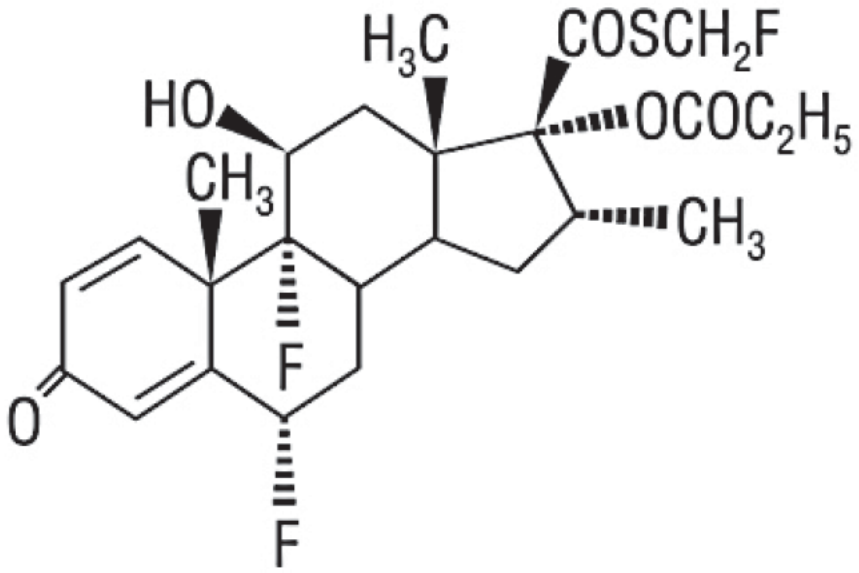
IND number: 77363
Review number: 01
Sequence number/date/type of submission: 000/April 2, 2007/ Initial IND
Stamped date: April 5, 2007
Information to sponsor: Yes () No (X)
Sponsor and/or agent: MedPointe Pharmaceuticals, MedPointe Healthcare Inc.
265 Davidson Avenue, Suite 300
Somerset, NJ 00873-4120
Reviewer name: Jean Q. Wu
Division name: Division of Pulmonary and Allergy Products
HFD #: 570
Review completion date: May 1, 2007

Drug:

Trade Name: N/A
Generic Name: Azelastine/Fluticason Combination Nasal Spray
Code name: (b) (4) Nasal Spray
Chemical name:
4-(4-Chloro-benzyl)-2-(1-methyl-azepan-4-yl)-3,4-dihydro-2H-phthal-azin-1-one Hydrochloride/S-(fluoromethyl)6alpha,9-difluoro-11beta-17-dihydroxy-16alpha-mthyl-3-oxoandrosta-1,4-diene-17beta-carbothioate,17-propionate
Molecular Formula/Molecular Weight:
Azelastine: $C_{22}H_{24}ClN_3O \cdot HCl/418.37$
Fluticasone: $C_{25}H_{31}F_3O_5S/500.6$
CAS Number: 79307-93-0/87474-14-2
Structure:
Azelastine Hydrochloride



Fluticasone Propionate



Relevant INDs/NDAs/DMFs: Astelin® (NDA 20-114), Flonase® (NDA20-121)

Drug class:

Azelastine: H_1-receptor antagonist; Fluticasone: corticosteroid

Intended clinical population: adults and children 12 years of age and older with nasal symptoms of allergic rhinitis

Clinical formulation:
Active drug: Azelastine Hydrochloride and Fluticasone Propionate.
Inactive ingredients: benzalkonium chloride (b) (4) glycerol (b) (4) polysorbate 80 (b) (4) microcrystalline cellulose and carboxymethylcellulose (b) (4) phenyl ethyl alcohol (b) (4) and purified water.
Each spray delivers Azelastine (b) (4) and Fluticasone 50 µg.

Route of administration: intranasal spray

Proposed clinical protocol:

(b) (4)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Previous clinical experience:
Astelin® was approved on November 1, 1996 and Flonase® was approved on October 19, 1994 in the US under NDA 20-114 and NDA 20-121, respectively. The recommended dose of Astelin® is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 year old and the recommended dose of Flonase® is either two 50 µg sprays in each nostril once daily or one 50 µg sprays in each nostril twice daily. The fixed-dose combination product (MP29-01), Duonase Nasal Spray, was approved in India in August 2004. (b) (4)

Studies reviewed within this submission: None

Studies not reviewed within this submission: The information of pharmacology and toxicology were referred to the individual Astelin® and Flonase® product information.

TABLE OF CONTENTS

2.6.2 PHARMACOLOGY

N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

N/A

2.6.6 TOXICOLOGY

N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

Astelin® (azelastine hydrochloride), a H_1-receptor antangoist, was approved on November 1, 1996 for the treatment of the nasal symptoms of seasonal allergic rhinitis and nonallergic vasomotor rhinitis in the US under NDA 20-114. The recommended dose of Astelin® is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 year old. Flonase® (fluticasone propionate), a synthetic, trifluorinated corticosteroid with anti-inflammatory activity, was approved on October 19, 1994 for the management of the nasal symptoms of seasonal/perennial allergic rhinitis and nonallergic vasomotor rhinitis in the US under NDA 20-121. The recommended dose of Flonase® is either two 50 µg sprays in each nostril once daily or one 50 µg sprays in each nostril twice daily in adults or one 50 µg spray once daily (starting dose) in pediatric patients (4 years and older).

The pharmacological and toxicological profile of individual drug product has been well characterized. [redacted] Glycerin (synonym: glycerol), has been used as an inactive ingredient in many approved products via various routes of administration. For the same route of administration in this application, the approved Nasonex Nasal Spray (mometasone furoate monohydrate) contains [redacted] glycerin/spray (COMIS database search result of NDA 20-762). At the recommended dose of Nasonex for allergic rhinitis in adults and children 12 years of age and older (two sprays per nostril once daily, i.e. 200 mcg/day), the glycerin level would be [redacted] mg/day. At the recommended dose of Nasonex for nasal polyp in adults 18 years of age and older (two sprays per nostril b.i.d, i.e. 400 mcg/day), the glycerin level would be [redacted] mg/day. The label of Nasonex® describes a clinical trial for allergic rhinitis with dose ranging from 50-800 mcg/day. The dose of 800 mcg/day is 4 times of the recommended dose for allergic rhinitis at which glycerin would be [redacted] mg/day. In the proposed single dose clinical study (one spray/nostril once daily), the glycerol level is [redacted] mg/day given the volume of each spray of 0.14 mL and the glycerol concentration of [redacted] The multiple dose clinical study protocols or synopsis were not submitted in this application.

However, in the development plan, the sponsor mentioned phase 3 clinical studies with duration of 2 or 4 weeks and dose of one spray/nostril twice daily in adults and adolescents 12 years of age and older. At the doses of the planned phase 3 clinical studies, the glycerol level would be (b) (4) which is within the range of glycerol level (b) (4) at the recommended dose of Nasonex for nasal polyps in adults, and within the range of glycerol level (b) (4) at the dose range in the Nasonex clinical trial for allergic rhinitis in adults and children 12 years of age and older.

The sponsor also indicated that 14-day local toxicity studies (b) (4) in dogs and rats are to be performed prior to conducting multiple dose clinical trials.

(b) (4) The fixed-dose combination product (MP29-01), Duonase Nasal Spray, has been on the market in India since 2004. The sponsor indicated that no serious or unanticipated adverse events have been reported to Cipla (Indian manufacturer and marketer of Duonase).

In the proposed single dose clinical study, the doses for both azelastine (one (b) (4) per nostril/dose) and fluticasone (one 50 µg spray per nostril/dose) are within the recommended dosages.

Recommendation: The proposed single dose clinical study is reasonably safe to proceed from the preclinical perspective.

Letter to the sponsor: N/A

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX 2

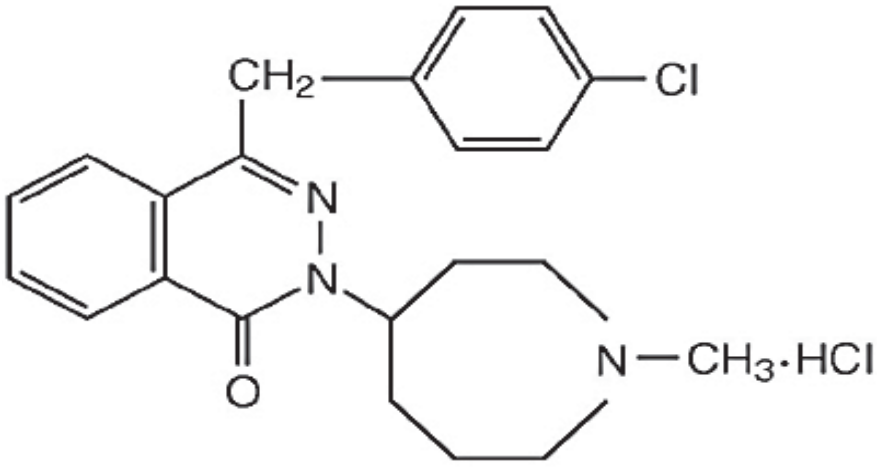
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

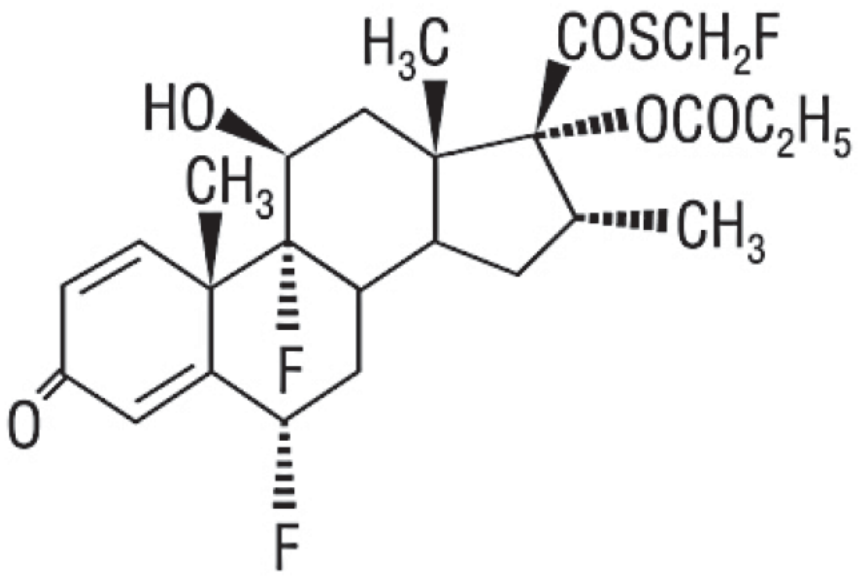
IND number: 77363
Review number: 02
Sequence number/date/type of submission: 009/December 13, 2007/PN, CMC, IT
Information to sponsor: Yes () No (X)
Sponsor and/or agent: MedPointe Pharmaceuticals, MedPointe Healthcare Inc.
265 Davidson Avenue, Suite 300
Somerset, NJ 00873-4120
Reviewer name: Jean Q. Wu
Division name: Division of Pulmonary and Allergy Products
HFD #: 570
Review completion date: July 2, 2008

Drug:

Trade Name: N/A
Generic Name: Azelastine/Fluticason Combination Nasal Spray
Code name: (b) (4) Nasal Spray
Chemical name:
4-(4-Chloro-benzyl)-2-(1-methyl-azepan-4-yl)-3,4-dihydro-2H-phthal-azin-1-one Hydrochloride/S-(fluoromethyl)6alpha,9-difluoro-11beta-17-dihydroxy-16alpha-mthyl-3-oxoandrosta-1,4-diene-17beta-carbothioate,17-propionate
Molecular Formula/Molecular Weight:
Azelastine: $C_{22}H_{24}ClN_3O \cdot HCl/418.37$
Fluticasone: $C_{25}H_{31}F_3O_5S/500.6$
CAS Number: 79307-93-0/87474-14-2
Structure:
Azelastine Hydrochloride



Fluticasone Propionate



Relevant INDs/NDAs/DMFs: Astelin® (NDA 20-114), Flonase® (NDA20-121)

Drug class:

Azelastine: H_1-receptor antagonist; Fluticasone: corticosteroid

Intended clinical population: adults and children 12 years of age and older with nasal symptoms of allergic rhinitis

Clinical formulation:

Active drug: Azelastine Hydrochloride and Fluticasone Propionate w/w).
Each metered spray delivers a 0.137 mL mean volume of suspension containing 137 µg of azelastine hydrochloride and 50 µg of fluticasone propionate.
See the table below (excerpted from CMC section, Vol 2, page 99, Item 7.d.2)

A full statement of the quantitative composition of Azelastine Hydrochloride 0.1% w/w and Fluticasone Propionate 0.0365% w/w Nasal Spray (Formulatio 29-02) is provided below.

Active Ingredients	% w/w	Amount/ (b) (4)
Azelastine Hydrochloride[1]	0.1	
Fluticasone Propionate, USP[1]	0.0365	
Inactive Ingredients		
Edetate Disodium, USP	(b) (4)	(b) (4)
Glycerin, USP		
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF (b) (4)		
Polysorbate 80, NF		
Benzalkonium Chloride, NF[1, 2]	0.01	
Phenylethyl Alcohol, USP	0.25	
Purified Water, USP[3] (b) (4)	(b) (4)	

Route of administration: intranasal spray

Proposed clinical protocol:
Protocol MP4001: "Randomized, Double-Blind Trial of MP29-02 Nasal Spray Compared to Placebo, Astelin Nasal Spray, and Fluticasone Propionate Nasal Spray in the Treatment of Seasonal Allergic Rhinitis." In this study, approximately 600 patients at 12 years of age or older will be randomized to treatment in a 1:1:1:1 ratio after a 7-day lead-in placebo treatment period. Patients will be treated for two weeks with 1) MP29-02 one spray per nostril bid, (548 µg azelastine and 200 µg fluticasone propionate per day); 2) Azelastine hydrychloride (Astelin) Nasal Spray 0.1% one spray per nostril bid (548 µg per day); 3) Fluticasone Propionate Nasal Spray, one spray per nostril bid (200 µg per day) or 4) Placebo nasal spray, one spray per nostril bid.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Previous clinical experience:
Astelin® was approved on November 1, 1996 and Flonase® was approved on October 19, 1994 in the US under NDA 20-114 and NDA 20-121, respectively. The recommended dose of Astelin® is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 year old and the recommended dose of Flonase® is either two 50 µg sprays in each nostril once daily or one 50 µg sprays in each nostril twice daily. The fixed-dose combination product (MP29-01), Duonase Nasal Spray, was approved in India in August 2004. (b) (4)

Studies reviewed within this submission:
1. A 14-Day Intranasal Toxicity Study with 0.1% Azelastine and 0.0365% Fluticasone in Sprague-Dawley Rats (Vol. 4, page 1)
2. A 14-Day Intranasal Toxicity Study with 0.1% Azelastine and 0.0365% Fluticasone in Beagle Dogs (Vol. 5, page 168)

Studies not reviewed within this submission: CMC Information (Vols 2-3)

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2.6.2 PHARMACOLOGY

N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

N/A

2.6.6 TOXICOLOGY

2.6.6.3 Repeat-dose toxicity

Study title: A 14-Day Intranasal Toxicity Study with 0.1% Azelastine and 0.0365% Fluticasone in Sprague-Dawley Rats

Key study findings:

- One dose of Azelastine and Fluticasone Nasal Spray was tested with each of reference drugs, Astelin and Flonase.
- Limited organs/tissues were examined microscopically for local toxicity evaluation.
- The body weight gain was reduced about 50% in the females treated with Azelastin/Fluticasone spray, Astelin or Flonase.
- The NOAEL was the only dose tested, 0.1% Azelastine and 0.0365% Fluticasone (0.4 mL/day = 0.4 mg Azelastine and 0.146 mg Fluticasone/day)
- No evidence suggested a potentiation of local toxicities due to the combination of Azelastin/Fluticasone.

Study no.: No. 0437RM57.006
Volume #, and page #: Vol. 4, page 4 – Vol. 5. page 166
Conducting laboratory and location: (b) (4)

Date of study initiation: June 18, 2007
GLP compliance: GLP statement indicated its GLP compliance
QA report: yes (X) no ( )
Drug, lot #, and % purity: (referenced from CoAs in Vol 4, pages 282-292)
Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, lot/batch# G7005, content of Azelastine Hydrochloride mean =99% (of label claim) and content of Fluticasone Propionate mean =99% (of label claim).
The reference drug 1, Astelin Nasal Solution, Lot No. 0000002940, content of Azelastine Hydrochloride mean = 98.4% of label claim per CoA.
The reference drug 2, Flonasal Spray, Lot No. C216353 (no CoA is provided in the report)

Methods

Doses, Number/sex/group or time point, Satellite groups used for toxicokinetics (TK) or recovery, and Route, formulation, volume, and infusion rate:

Group No./Treatment	Dose Volume*	No. of Animals	
		Males	Females
1. Control	0.1 ml/nostril	10	10
2. Vehicle	0.1 ml/nostril	10	10
3. Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray	0.1 ml/nostril	10	10
4. Astelin Nasal Spray	0.1 ml/nostril	10	10
5. Flonase Nasal Spray	0.1 ml/nostril	10	10

As shown in the study design table (excerpted from Vol. 4, page 13) above, the animals in each group were dosed intranasally twice per day for 14 days. No TK or recovery groups were assigned.

Formulation:

The test article Azelastine and Fluticasone Nasal Spray is a white homogenous redispersable suspension free from visible foreign material. The vehicle control is the placebo of the test article. (b) (4)

Species/strain: Crl: CD® (SD) Rat (b) (4)

Age: Approximately 8 weeks at initiation of dosing

Weight: males: 228-278 g, females: 173-220 g

Observation and Times:

Clinical signs: Cage-side observation was performed twice daily (am and pm) through the treatment period for mortality/morbidity check. Clinical observation was conducted prior to dose and at least once post dose (approximately one hour post dose) on Day 1 and Day 14, and once prior to the scheduled termination on Day 15.

Body weights: Body weight was recorded at randomization, prior to dosing on Days 1 and 8, following the final dose on Day 14 and prior to termination on Day 15 (fasted).

Food consumption: Food consumption was recorded weekly from Day 1 through the scheduled termination.

Hematology, Clinical chemistry, Coagulation and Urinalysis: Samples from all animals were collected at the scheduled termination on Day 15.

Gross pathology: All surviving animals were necropsied on Day 15, following 14-day consecutive dosing. Complete macroscopic examinations were performed on all necropsied animals.

Organ weights: The tissues/organs listed in the table below were weighed.

Adrenals	Pituitary Gland
Brain	Prostate
Heart	Spleen
Kidneys	Testes
Liver	Tracheobronchial lymph nodes
Lung with trachea	Thymus
Ovaries	Thyroid/parathyroid
Pancreas	Uterus

Histopathology: A full panel of tissues from each animal was preserved in 10% netural-buffered formalin, Davidson's solution (eyes) or Bouin's solution (testes). The following tissues from all necropsied animals were microscopically examined.

Nasal cavity/turbinates	Adrenals
Nasopharynx	Sternum with bone marrow
Larynx	Liver
Trachea	Lymph nodes, mandibular and mesenteric
Lung with mainstem bronchus	Pituitary
Tracheobronchial lymph nodes	Spleen
Gross lesions	Thymus
	Thyroid/parathyroid

Adequate Battery: yes (x), no ( )—explain
Peer review: yes ( ), no (x)

Toxicokinetics: Not performed.

Results:

Mortality: There was no mortality or moribund sacrifice observed in the study.

Clinical signs: There were no treatment related clinical signs of toxicity.

Body weights: In males, there were no significant difference in mean body weight or body weight change observed between control, vehicle control and the treated groups. In females, the percent body weight gain over 14 days were approximately 50% lower in the test article treated group (7.3%), Azelastine treated group (7.5%) and Fluticasone treated group (7.0%) when compared to the saline control (14%) and vehicle control (15%) groups .

Food consumption: There were no significant changes in food consumption attributed to the test article or reference drugs.

Hematology, Clinical chemistry, Coagulation and Urinalysis: There were no significant test article or reference drug related effects on clinical pathology. The slight increase in glucose and calcium (<20%) observed in the test article treated females were not considered toxicological significant.

Gross pathology: There were no gross findings noted at necropsy attributed to the treatment with the test article or reference drugs.

Organ weights: There were no significant treatment related effects on organ weight. The decrease of thymus weight (absolute and relative to brain) in the female Flonase treated group was less than 30% and lacked corresponding histology finding, hence, was not considered toxicologically significant.

Histopathology: There were no significant test article-related findings in the examined tissues. As shown in the table below, the acute and/or subacute nasal cavity hemorrhage was observed in vehicle and Astelin treated males and in vehicle, test article, Astelin and

Flonase treated females. Its severity was minimal and the incidence was low overall (with a slightly higher incidence in the teat article treated female compared to the vehicle). The findings were considered clinically monitorable. The atelectasis were observed in all groups and were not considered toxicological significant.

Findings	Males					Female				
Dose Groups	1	2	3	4	5	1	2	3	4	5
Hemorrhage, Nasal Cavity Acute, focal	0	0	0	1(1)	0	0	0	**3(1)**	1(1)	0
Hemorrhage, Nasal Cavity Acute, multifocal	0	0	0	0	0	0	0	1(1)	0	1(1) 1(1)
Hemorrhage, Nasal Cavity subcute, multifocal	0	1(1)	0	0	0	0	1(1)	0	0	0
Hemorrhage, acute, focal and multifocal, Lung	0	0	0	0	1(1)	1(2)	2(1) 1(2)	2(1) 1(2)	2(1)	 1(2)
Atelectasis, focal and multifocal, Lung	1(1) 5(2)	3(1) 1(2) 1(3)	1(1) 5(2) 2(3)	4(1) 4(2)	2(1) 3(2) 1(4)	5(1) 1(2)	1(1) 2(2) 1(3)	2(1) 3(2) 3(3)	3(2) 3(3) 1(4)	2(1) 3(2) 1(4)

* Group 1- control, Group 2- Vehicle control, Group 3- Azelastine/Fluticasone, Group 4 – Astelin, Group 5 –Flonase; n=10/group
Note: the number in the parenthese means the level of severity: 1-minimal, 2-slight, 3-moderate, 4-marked

Study title: A 14-Day Intranasal Toxicity Study with 0.1% Azelastine and 0.0365% Fluticasone in Beagle Dogs

Key study findings:

- One dose level of Azelastine/Fluticasone Nasal Spray, Astelin Nasal Spray or Flonase Nasal Spray was tested.
- Limited organs/tissues were examined microscopically for local toxicity evaluation.
- A slight increase of incidence or severity in larynx mucosa-associated lymphoid tissue hyperplasia was observed in the Azelastin/Fluticasone, Astelin or Flonase treated groups. No evidence suggested a potentiation of local toxicities due to the combination of Azelastin/Fluticasone.

Study no.: No. 0437DM57.007
Volume #, and page #: Vol. 5 Page 168 – Vol. 6. Page 236
Conducting laboratory and location: (b) (4)

Date of study initiation: June 18, 2007
GLP compliance: GLP compliance statement included
QA report: yes (X) no ( )
Drug, lot #, and % purity: (referenced from CoAs in Vol 6, pages 135-149) Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, lot/batch# G7005, content of Azelastine Hydrochloride mean =99% (of label claim) and content of Fluticasone Propionate mean =99% (of label claim).

The reference drug 1, Astelin Nasal Solution, Lot No. 0000002940, content of Azelastine Hydrochloride mean = 98.4% of label claim per CoA.
The reference drug 2, Flonasal Spray, Lot No. C216353 (no CoA is provided in the report)

Methods

Doses, Number/sex/group or time point, Satellite groups used for toxicokinetics (TK) or recovery, and Route, formulation, volume, and infusion rate:

Group No./Treatment	Dose Volume*	No. of Animals	
		Males	Females
1. Control	0.1 ml/nostril	3	3
2. Vehicle	0.1 ml/nostril	3	3
3. Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray	0.1 ml/nostril	3	3
4. Astelin Nasal Spray	0.1 ml/nostril	3	3
5. Flonase Nasal Spray	0.1 ml/nostril	3	3

As shown in the study design table (excerpted from Vol. 5, page 177) below, the animals in each group were dosed intranasally twice per day for 14 days. No TK or recovery groups were assigned.

Formulation:
The test article Azelastine and Fluticasone Nasal Spray is a white homogenous redispersable suspension free from visible foreign material. The vehicle control is the placebo of the test article. (b) (4)

Species/strain: *Canis familiaris*, Beagle dog (b) (4)
Age: Approximately 5 months at initiation of dosing
Weight: males: 6.0-8.8 kg, females: 5.6-7.5 kg

Observation and Times:

Clinical signs: Cage-side observation was performed twice daily (am and pm) through the treatment period for mortality/morbidity check. Clinical observation was conducted prior to dose and at least once post dose (approximately one hour post dose) on Day 1 and Day 14, and once prior to the scheduled termination on Day 15.
Body weights: Body weight was recorded at randomization, prior to dosing on Days 1 and 8, following the final dose on Day 14 and prior to termination on Day 15 (fasted).
Food consumption: Food consumption was recorded daily from Day 1 through the scheduled termination.
Hematology, Clinical chemistry, Coagulation and Urinalysis: Samples from all animals were collected prior to the initial treatment and prior to the scheduled termination on Day 15.
Gross pathology: All surviving animals were necropsied on Day 15, following 14-day consecutive dosing. Complete macroscopic examinations were performed on all necropsied animals.
Organ weights: The tissues/organs listed in the table below were weighed.

Adrenals	Pituitary Gland
Brain	Prostate
Heart	Spleen
Kidneys	Testes
Liver	Tracheobronchial lymph nodes
Lung with trachea	Thymus
Ovaries	Thyroid/parathyroid
Pancreas	Uterus

Histopathology: A full panel of tissues from each animal was preserved in 10% netural-buffered formalin, Davidson's solution (eyes) or Bouin's solution (testes). The following tissues from all necropsied animals were microscopically examined.

Nasal cavity/turbinates	Adrenals
Nasopharynx	Sternum with bone marrow
Larynx	Liver
Trachea	Lymph nodes, mandibular and mesenteric
Lung with mainstem bronchus	Pituitary
Tracheobronchial lymph nodes	Spleen
Gross lesions	Thymus
	Thyroid/parathyroid

Adequate Battery: yes (x), no ( )—explain
Peer review: yes ( ), no (x)
Toxicokinetics: Not performed.

Results:
Mortality: There was no mortality or moribund sacrifice observed in the study.

Clinical signs: There were no treatment related clinical signs of toxicity.
Body weights: There were no treatment related effects on body weight and body weight gain.

Food consumption: There were no treatment related effects on food consumption.

Hematology, Clinical chemistry, Coagulation and Urinalysis: There were no treatment-related clinical pathology findings.

Gross pathology: There were no treatment-related findings in gross pathology evaluation.

Organ weights: There were no treatment-related effects on organ weight.

Histopathology: As listed in the table below, larynx hyperplasia of mucosa-associated lymphoid tissue was noted in test article treated males and females, and in saline control, Astelin and Flonase treated females. The incidence in treated groups was slightly higher than the saline control group. The finding maybe related to the Astelin, Flonase or the combination treatment. There were no other test article-related toxic findings observed in the evaluated tissues.

Findings	Males					Female				
Dose Groups	1	2	3	4	5	1	2	3	4	5
Hyperplasia, mucosa-associated lymphoid tissue, Larynx	0	0	1(3)	0	0	1(2)	0	**1(1) 1(2)**	2(1)	2(1)
Hyperplasia, mucosa-associated lymphoid tissue, Nasopharynx	0	0	0	0	1(2)	0	0	0	0	0
Alveolus macrophage infiltration, Lung multifocal	1(1)	0	0	1(1)	1(1) 1(2)	0	0	0	0	2(1)
Acute inflammation, Unilateral focal duct, Nasal turbinates, level 1-3	0	0	0	0	0	0	0	0	1(1-2)	0
Necrosis, hepatocellular, focal, Liver	0	0	0	0	0	0	0	0	0	1(1)

* Group 1- control, Group 2- Vehicle control, Group 3- Azelastine/Fluticasone, Group 4 – Astelin, Group 5 –Flonase; n=10/group
Note: the number in the parenthese means the level of severity: 1-minimal, 2-slight, 3-moderate, 4-marked

2.6.7 TOXICOLOGY TABULATED SUMMARY

N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

Astelin® (azelastine hydrochloride), a H_1-receptor antangoist, was approved on November 1, 1996 for the treatment of the nasal symptoms of seasonal allergic rhinitis and nonallergic vasomotor rhinitis in the US under NDA 20-114. The recommended dose of Astelin® is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 year old. Flonase® (fluticasone propionate), a synthetic, trifluorinated corticosteroid with anti-inflammatory activity, was approved on October 19, 1994 for the management of the nasal symptoms of seasonal/perennial allergic rhinitis and nonallergic vasomotor rhinitis in the US under NDA 20-121. The recommended dose of Flonase® is either two 50 µg sprays in each nostril once daily or one 50 µg sprays in each nostril twice daily in adults or one 50 µg spray once daily (starting dose) in pediatric patients (4 years and older).

The pharmacological and toxicological profile of two individual active ingredients has been well characterized. The sponsor conducted 14-day rat and dog studies to compare the combination drug product with each individual marketed product. Only one dose level of the combination drug was tested and the selected/limited tissues were examined microscopically for local toxicity evaluation. There were no clear treatment-related toxicities observed in both rat and dog studies. The larynx mucosa-associated lymphoid tissue hyperplasia maybe related to the treatment of combination drug or Astelin or Flonase alone. However, no evidence suggested a potentiation of local toxicities due to the combination of two drugs in these two studies.

In the current submission, the proposed doses for azelastine (137 µg/nostril bid=540 µg/day) and fluticasone (50 µg/nostril bid=200 µg/day) of MP29-02 in the 14-day clinical protocol (MP-4401) are still within the range of the recommended dosages of the approved products, Astelin and Flonase. At the proposed doses, the inactive ingredient, glycerol, would be (b) (4) based on (b) (4) which is within the range of glycerol level (b) (4) at the recommended dose of Nasonex® for nasal polyps in adults, and within the range of glycerol level (b) (4) at the dose range in the Nasonex® clinical trial for allergic rhinitis in adults and children 12 years of age and older. Hence, from the preclinical perspective, there are no significant safety concerns regarding the proposed clinical study.

Recommendation: No action indicated.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX 3

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	77,363
Supporting document/s:	SDN35
Sponsor's letter date:	June 15, 2010
CDER stamp date:	June 16, 2010
Product:	Azelastine/Fluticasone Nasal Spray
Indication:	Allergic rhinitis in adults and children 12 years of age and older
Sponsor:	Meda Pharmaceuticals, Inc. 265 Davidson Ave, Suite 300 Somerset, NJ 08873-4120
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Marcie L. Wood, Ph.D.
Supervisor/Team Leader:	Molly Topper, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Philantha Bowen

Template Version: December 7, 2009

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1 Executive Summary

1.1 Recommendations

1.1.1 Clinical Study (ies) Safe to Proceed: Yes/No

No clinical protocols were included in this submission (SDN35).

1.1.2 If Not Safe to Proceed, Recommendations to Allow Clinical Study (ies) to Proceed

Not applicable

1.1.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) *if any.*

We have reviewed your IND submission of June 16, 2010 (SDN35) and have the following nonclinical comments and requests for information:

1. Histopathological examination was conducted on only a partial battery of tissues in the rat 3-month intranasal toxicity study (0470RM57.001). Provide results of microscopic examination of the following tissues for all treatment groups in order to fully characterize the microscopic effects of the azelastine and fluticasone combination in rats: Aorta, brain, cervix, epididymides, esophagus, eye/optic nerve, fallopian tube, gall bladder, heart, kidneys, large intestines, ovaries, pancreas, prostate, salivary gland, seminal vesicles, small intestines, stomach, testes, urinary bladder, uterus, and vagina.

1.2 Brief Discussion of Nonclinical Findings

Toxicology studies (up to 14-days duration in rats and dogs) have been conducted with azelastine/fluticasone nasal spray under IND 77,363 and support clinical dosing with the combination product up to 14 days. In the current submission, the sponsor conducted a 3-month intranasal toxicity study to compare the azelastine/fluticasone combination nasal spray with the Astelin (azelastine) and fluticasone propionate marketed monoproducts. Only one dose of the azelastine/fluticasone combination (0.1% azelastine and 0.0365% fluticasone propionate; 0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day) was tested, and control (0.9% sodium chloride) and placebo (vehicle) groups were also included. Azelastine systemic exposure in the combination azelastine/fluticasone treatment group was lower than the Astelin group for males and females on Days 1 and 91. Fluticasone propionate was not detected in the plasma of the combination treatment group or the fluticasone propionate monoproduct group. Body weight was decreased in males and females in the azelastine/fluticasone (-7 and -9% for males and females, respectively) and fluticasone propionate (-6 and -15%

for males and females, respectively) groups on Day 91 versus controls. Body weight gain was also decreased in males and females in the azelastine/fluticasone (-10 and -17% for males and females, respectively) and fluticasone propionate (-9 and -29% for males and females, respectively) groups (Days 1-91) versus controls. Mast cells were increased in the mesenteric lymph nodes in the azelastine/fluticasone (9/10 males and 10/10 females) and fluticasone propionate (7/10 males and 8/10 females) groups versus controls. This increase was attributed to effects of fluticasone propionate. Mast cells were also increased in the mandibular lymph nodes of males and females in the azelastine/fluticasone group only versus control, vehicle, and monoproduct groups. The toxicological significance of this finding is uncertain.

The NOAEL was determined to be the only dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day). Increased mast cells in the mandibular lymph node in the azelastine/fluticasone combination group versus control and monoproduct groups are of uncertain toxicological relevance as they were also found at high background levels in the tracheobronchial lymph nodes of control males.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

79307-93-0/87474-14-2

2.1.2 Generic Name

Azelastine/Fluticasone Nasal Spray

2.1.3 Code Name

(b) (4) Nasal Spray

2.1.4 Chemical Name

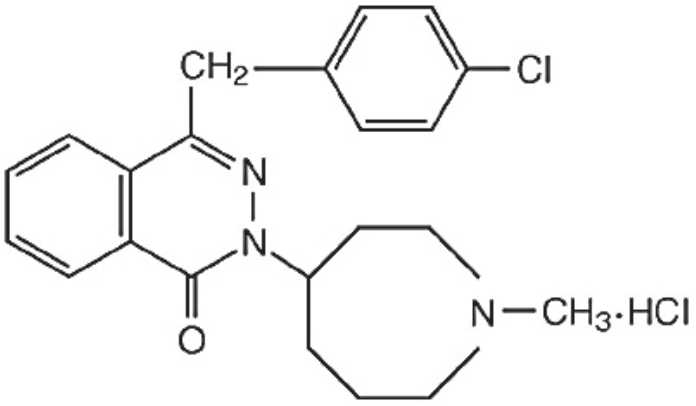
4-(4-Chloro-benzyl)-2-(1-methyl-azepan-4-yl)-3,4-dihydro-2H-phthal-azin-1-one Hydrochloride/S-(fluoromethyl)6alpha,9-difluoro-11beta-17-dihydroxy-16alpha-methyl-3-oxoandrosta-1,4-diene-17beta-carbothioate,17-propionate

2.1.5 Molecular Formula/Molecular Weight

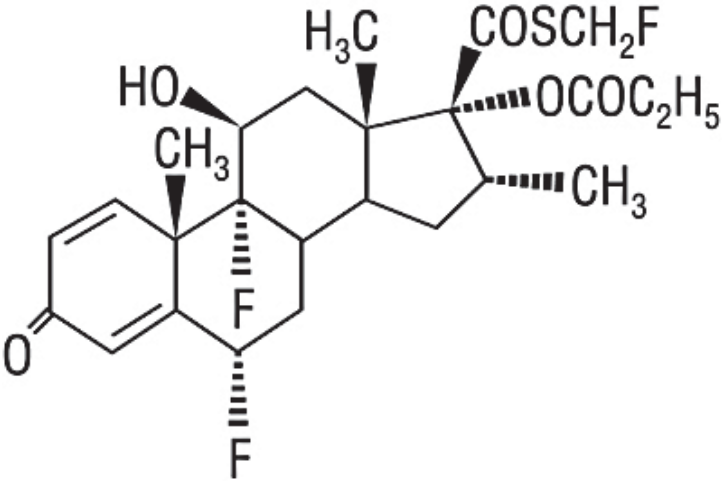
Azelastine: $C_{22}H_{24}ClN_3O \bullet HCl$/418.37
Fluticasone: $C_{25}H_{31}F_3O_5S$/500.6

2.1.6 Structure

Azelastine Hydrochloride



Fluticasone Propionate



2.1.7 Pharmacologic class

Azelastine: H_1-receptor antagonist
Fluticasone: corticosteroid

2.2 Relevant IND/s, NDA/s, and DMF/s

Astelin (NDA 20-114), Flonase (NDA 20-121)

2.3 Clinical Formulation

2.3.1 Drug Formulation

Not applicable. No clinical protocols were included in this submission.

2.3.2 Comments on Novel Excipients

Not applicable

2.3.3 Comments on Impurities/Degradants of Concern

Not applicable

2.4 Proposed Clinical Population and Dosing Regimen

No clinical protocols were included in this submission (SDN35).

2.5 Regulatory Background

2.5.1 Previous Clinical Experience

Astelin was approved on November 1, 1996 and Flonase was approved on October 19, 1994 in the US under NDA 20-114 and NDA 20-121, respectively. The recommended dose of Astelin is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 years of age (Astelin approved label, April 2007), and the recommended dose of Flonase is either two 50 µg sprays in each nostril once daily or one 50 µg spray in each nostril twice daily (starting dose in pediatric patients 4 years of age and older; Flonase approved label, March 2004). The fixed-dose combination product (MP29-01), Duonase Nasal Spray, was approved in India in August 2004.

Previous clinical experience under IND 77,363 includes (b) (4) a multiple dose (14-day) study of 1) MP29-02, one spray per nostril bid (548 µg azelastine and 200 µg fluticasone propionate per day), 2) Astelin nasal spray, one spray per nostril bid (548 µg azelastine per day), Fluticasone Propionate nasal spray, one spray per nostril bid (200 µg fluticasone per day), or placebo nasal spray, one spray per nostril bid, under clinical protocol MP4001.

2.5.2 History of Regulatory Submission

Meda Pharmaceuticals is studying azelastine/fluticasone combination nasal spray for the treatment of allergic rhinitis in children and adults 12 years of age and older. In the Original IND 77,363 submission (dated April 2, 2007), the sponsor proposed (b) (4) In SDN 9 (dated December 13, 2007), the sponsor proposed a multiple dose (14-day) study of 1) MP29-02, one spray per nostril bid (548 µg azelastine and 200 µg fluticasone propionate per day), 2) Astelin nasal spray, one spray per nostril bid (548 µg azelastine per day), Fluticasone Propionate nasal spray, one spray per nostril bid (200 µg fluticasone per day), or placebo nasal spray, one spray per nostril bid, under

clinical protocol MP4001. Clinical protocol MP4001 was accompanied by pivotal 14-day repeat-dose toxicity studies in rats and dogs, which provided adequate nonclinical support for the proposed study. Both clinical studies were allowed to proceed.

In this general review, the reviewer is providing a detailed evaluation of a 3-month intranasal toxicity study with azelastine and fluticasone in rats.

3 Studies Submitted

3.1 Studies Reviewed

Study no. 0470RM57.001, "A 90-day intranasal toxicity study with azelastine and fluticasone in Sprague-Dawley Rats."

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Nonclinical reviews by Dr. Jean Q. Wu for IND 77,363 dated May 1, 2007 and July 2, 2008.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A 90-day intranasal toxicity study with azelastine and fluticasone in Sprague-Dawley rats

Study no.:	0470RM57.001
Study report location:	SDN35, volumes C1-5
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 8, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Azelastine/Fluticasone, Lot # G70454, mean content of azelastine hydrochloride = 99% of label claim, mean content of fluticasone propionate = 102% of label claim; Fluticasone Propionate Nasal Spray, Lot/Batch # 857415A/756855A, no CoA provided in report; Astelin Nasal Spray, Lot # 0000004307, mean content of azelastine hydrochloride = 98.2% of label claim

Key Study Findings

- One dose of the combination azelastine/fluticasone nasal spray (0.1% azelastine and 0.0365% fluticasone propionate; 0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day) was tested with the monoproduct reference drugs Astelin and fluticasone propionate. Control (0.9% sodium chloride) and vehicle (placebo of test article) groups were also included.
- Azelastine systemic exposure in the combination azelastine/fluticasone treatment group was lower than the Astelin group for males and females on Days 1 and 91. Fluticasone propionate was not detected in the plasma of the combination treatment group or the fluticasone propionate monoproduct group.
- Body weight was decreased in males and females in the azelastine/fluticasone (-7 and -9% for males and females, respectively) and fluticasone propionate (-6 and -15% for males and females, respectively) groups on Day 91 versus controls. Body weight gain was also decreased in males and females in the azelastine/fluticasone (-10 and -17% for males and females, respectively) and fluticasone propionate (-9 and -29% for males and females, respectively) groups (Days 1-91) versus controls.
- Mast cells were increased in the mesenteric lymph nodes in the azelastine/fluticasone (9/10 males and 10/10 females) and fluticasone propionate (7/10 males and 8/10 females) groups versus controls. This increase was attributed to effects of fluticasone propionate. Mast cells were also increased in the mandibular

lymph nodes of males and females in the azelastine/fluticasone group only versus control, vehicle, and monoproduct groups. The toxicological significance of this finding is uncertain.

- The NOAEL was the only combination dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day).
- Findings suggested no potentiation of toxicities due to the azelastine/fluticasone combination.

Methods	
Doses:	Control (0.9% sodium chloride), vehicle (placebo of test article), Azelastine/Fluticasone (0.4 mg azelastine/day and 0.146 mg fluticasone/day, Astelin, and Fluticasone Propionate
Frequency of dosing:	Twice daily for 91 days
Route of administration:	Intranasal
Dose volume:	0.1 mL/nostril at each dosing session = 0.4 mL/day
Formulation/Vehicle:	Placebo of test article
Species/Strain:	Sprague Dawley rat (Crl:CD(SD))
Number/Sex/Group:	10/sex/group for the main toxicology study
Age:	Approximately 6.5 weeks old at initiation of dosing
Weight:	Males: 171-224 g; Females: 129-181 g (Day 1 study weights)
Satellite groups:	The following animals were assigned for toxicokinetics: 3/sex for control and vehicle groups, 9/sex for the Azelastine/Fluticasone group, and 6/sex for the Astelin and Fluticasone Propionate groups. A recovery group was not included.
Unique study design:	See below
Deviation from study protocol:	Only minor deviations occurred

Observations and Results

Mortality

Animals were observed twice daily for mortality/morbidity through Day 91 (Toxicology and TK animals) and once prior to sacrifice on Day 92 (Toxicology animals only). All Toxicology animals survived until their scheduled sacrifice. One TK male and one TK female in the azelastine/fluticasone group died on Day 91 and Day 88, respectively. The TK male died immediately after blood collection, presumably due to procedural stress.

The cause of death for the TK female was not evident. The sponsor considered both deaths to be unrelated to test article administration.

Clinical Signs

Toxicology animals were observed for clinical signs pre-dose and a minimum of once post-dose (approximately 1-2 hrs post each dose) on Days 1-91 and once prior to sacrifice on Day 92. Special attention was paid to nasal observations. Clinical signs were not recorded for TK animals. No treatment-related clinical signs of toxicity were observed.

Body Weights

Body weights were recorded at randomization/selection, pre-dose on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85 (weekly for both Toxicology and TK animals), and following the last dose on Day 91 (Toxicology animals only). Fasted body weight was also recorded prior to sacrifice on Day 92 (Toxicology animals only). Body weight was decreased in males and females in the azelastine/fluticasone (-7 and -9% for males and females, respectively) and fluticasone propionate (-6 and -15% for males and females, respectively) groups on Day 91 versus controls. Body weight gain was also decreased in males and females in the azelastine/fluticasone (-10 and -17% for males and females, respectively) and fluticasone propionate (-9 and -29% for males and females, respectively) groups (Days 1-91) versus controls. Decreased body weight is characteristic of glucocorticoids.

Feed Consumption

Feeder weight was recorded weekly for Toxicology animals only. No treatment-related changes in food consumption were observed.

Ophthalmoscopy

Ophthalmological exams were performed on all animals (Toxicology and TK) prior to initiation of treatment and during the final week of treatment (Toxicology animals only). Dilating agent (0.5% tropicamide) was instilled into eyes before examinations, and indirect ophthalmoscopy exams were performed by a consulting veterinary ophthalmologist. Striate retinopathy was observed in the left eye of one azelastine/fluticasone female (animal no. 2573) during the pre-terminal exam; however, the veterinary ophthalmologist stated that this lesion has no toxicological significance. In general, the reviewer agrees with the sponsor's assessment, as retinal degeneration in rats and mice may occur secondary to uveitis or excessive light exposure and does not affect functional vision unless retinal changes are extensive[1]. However, it is also noted that the following eye changes were observed in clinical trials with Flonase: dryness and

[1] Slatter, DH. (2001). Differential Diagnosis of Common Ocular Diseases and Syndromes. In R. Kersey and D. LeMelledo (Eds.), Fundamentals of Veterinary Ophthalmology (pp. 571-608). Philadelphia, PA: Elsevier.

irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts (Flonase approved label, March 2004).

ECG

Not performed

Hematology

Blood samples were collected from fasted, CO_2-anesthetized Toxicology animals by cardiocentesis at the terminal sacrifice on Day 92. A complete battery of hematology and coagulation parameters was analyzed. WBC were decreased in fluticasone propionate males and females by -21 and -53%, respectively (the decrease in females was statistically significant), versus controls. Absolute and relative lymphocytes were statistically significantly decreased in fluticasone propionate females (-57 and -8%, respectively) versus controls. Relative neutrophils were statistically significantly increased in fluticasone propionate females (72%) versus controls. [*Reviewer's note: The sponsor stated that these values are within normal historical limits for the lab; however, decreased WBC and lymphocytes and increased neutrophils were also attributed to fluticasone in inhalation toxicity studies in rats in NDA 21-077 (Advair Diskus Pharmacology review, March 2000)].* There were no notable findings in red blood cell morphology or coagulation parameters in any study group.

Clinical Chemistry

Blood samples were collected from fasted, CO_2-anesthetized Toxicology animals by cardiocentesis at the terminal sacrifice on Day 92. A complete battery of clinical chemistry parameters was analyzed. Treatment-related changes in clinical chemistry parameters versus controls, which occurred in females only, are presented in the table below. [*Reviewer's note: The sponsor stated that these values, with the exception of ALT, are within normal historical limits for the lab. In addition, the sponsor did not consider the ALT changes in azelastine/fluticasone and fluticasone propionate females to be biologically significant; however, increased ALT, as well as increased AST, cholesterol, and triglycerides were attributed to fluticasone in inhalation toxicity studies in rats in NDA 21-077 (Advair Diskus Pharmacology review, March 2000)].*

Table 1: Clinical chemistry findings in a 3-month intranasal toxicity study of azelastine and fluticasone in rats

Clinical Chemistry Parameter (Day 92)	Treatment group (% change)					
	Males			Females		
	3	4	5	3	4	5
Total bilirubin	-	-	-	23*	-	-
AST	-	-	-	81*	-	122*
ALT	-	-	-	207*	-	201*
Cholesterol	-	-	-	31	-	28
Triglycerides	-	-	-	36*	-	22

Treatment groups: 3 = azelastine/fluticasone propionate; 4 = Astelin; 5 = fluticasone propionate

* Statistically significant
- No noteworthy change

Urinalysis

Urine samples were collected in metabolism cages from fasted Toxicology animals overnight (approximately 12-18 hrs) prior to the terminal sacrifice on Day 92. A complete battery of urinalysis parameters was analyzed. No treatment-related changes in quantitative or qualitative urinalysis parameters were observed.

Gross Pathology

Animals were euthanized by CO_2 asphyxiation on Day 92. A complete necropsy was performed on all Toxicology animals. Necropsy examinations included examination of external body surfaces, all orifices, and the cranial, thoracic, and abdominal cavities and their contents. No treatment-related macroscopic findings were observed.

Organ Weights

The following organs from Toxicology animals were weighed before fixation (paired organs were weighed together): adrenals, brain, epididymides, heart, kidneys, liver, lungs with trachea, ovaries, pancreas, pituitary gland, prostate, spleen, testes, thymus, and thyroid/parathyroid. Organ-to-body and organ-to-brain weight ratios were calculated using the final body weight recorded prior to necropsy. Absolute organ weight changes, as well as organ weight changes relative to body and brain weight are given in the following table. Both absolute and spleen weight relative to brain weight were statistically significantly decreased in azelastine/fluticasone and fluticasone propionate females (spleen weights were also decreased in inhalation toxicity studies in fluticasone-treated rats in NDA 21-077 (Advair Diskus Pharmacology review, March 2000). Absolute kidney weight was also decreased in azelastine/fluticasone males and females and fluticasone propionate females. Despite the slight changes in organ weights given below, there were no corresponding treatment-related microscopic changes.

Table 2: Percent organ weight changes in a 3-month intranasal toxicity study of azelastine and fluticasone propionate in rats

Tissue	Treatment group (% change)					
	Males			Females		
	3	4	5	3	4	5
Brain, absolute	-	-	-	-	-	-
% BW	-	-	-	-	-	18*
% BRW	-	-	-	-	-	-
Heart	-	-	-	-	-	-
% BW	-	-	-	-	-	20*
% BRW	-	-	-	-	-	-
Kidneys, absolute	-16*	-	-	-10*	-	-9*
% BW	-	-	-	-	-	-
% BRW	-	-	-	-	-	-
Liver, absolute	-	-	-	-	-	13*

Tissue	Treatment group (% change)					
	Males			Females		
	3	4	5	3	4	5
% BW	-	-	-	-	-	-
% BRW	-	-	-	-	-	-
Lung w/bronchi, absolute	-	-	-	-	-	-
% BW	-	-	-	-	-	15*
% BRW	-	-	-	-	-	-
Spleen	-14	-	-	-22*	-	-23*
% BW	-	-	-	-15	-	-
% BRW	-	-	-	-20*	-	-21*

Treatment groups: 3 = azelastine/fluticasone propionate; 4 = Astelin; 5 = fluticasone propionate
* Statistically significant
- No noteworthy change

Histopathology

Adequate Battery

The following tissues from Toxicology animals were preserved in 10% formalin (with the exception of the eyes and testes, which were preserved in Davidson's fixative and Bouin's fixative, respectively): aorta, heart, digestive tract [salivary glands, tongue, esophagus, stomach, small intestine (duodenum, jejunum, ileum), large intestine (cecum, colon, rectum), pancreas, liver*], respiratory tract (nasal cavity/turbinates*, nasopharynx*, larynx*, trachea*, lung with mainstem bronchus*, tracheobronchial lymph nodes*), lymphoid/hematopoietic tissues [sternum with bone marrow*, thymus*, spleen*, lymph nodes (mandibular*, mesenteric*)], kidneys, urinary bladder, ovaries, uterus, cervix, vagina, testes, epididymides, prostate, seminal vesicles, adrenals*, pituitary*, thyroid/parathyroid*, skin, mammary gland, skeletal muscle, femur with articular surface, eye with optic nerve, harderian gland, sciatic nerve, brain, spinal cord (cervical, midthoracic, lumbar), lacrimal glands, zymbal's gland, gross findings*, and bone marrow smear. Tissues selected for microscopic evaluation (designated by *) were processed in paraffin, sectioned, and stained with hematoxylin and eosin. [*Reviewer's note: The sponsor examined only a partial battery of tissues. A complete battery of tissues should be examined in order to fully characterize the microscopic effects of the combination of azelastine and fluticasone in the rat*].

Peer Review

A peer review was not performed.

Histological Findings

Microscopic findings in the rat are presented in the following table. See Section 11 below for a discussion of findings (Integrated Summary and Safety Evaluation).

Table 3: Microscopic changes in a 3-month intranasal toxicity study of azelastine and fluticasone propionate in rats

Tissue	Treatment group									
	Males					Females				
	1	2	3	4	5	1	2	3	4	5
Mandibular LN, n=10/sex										
-Mast cells, increased	1 (1)	2 (1)	**5** (1)	2 (1.5)	2 (1)	2 (1.5)	2 (1)	**5** (1.2)	2 (1)	1 (2)
-Lymphoid hyperplasia	1 (2)	1 (2)	2 (1)	2 (2)	1 (2)	3 (2)	3 (1.7)	1 (1)	5 (1.6)	3 (1.7)
Mesenteric LN, n=10/sex										
-Mast cells, increased	0	0	**9** (2.2)	0	**7** (2.4)	0	0	**10** (2.3)	0	**8** (2.5)
Tracheobronchial LN, n=10/sex										
-Mast cells, increased	4 (1.5)	2 (1)	4 (1.5)	1 (1)	3 (1.3)	0	1 (1)	4 (1.5)	1 (1)	1 (1)

Treatment groups: 1 = control; 2 = vehicle; 3 = azelastine/fluticasone propionate; 4 = Astelin; 5 = fluticasone propionate
( ) Indicates average severity of findings: 1 = minimal, 2 = slight/mild, 3 = moderate

Special Evaluation

None

Toxicokinetics

For control and vehicle groups, blood (~0.5 mL/sample) was collected from CO_2-anesthetized animals (3/sex/group) via retroorbital puncture at pre-dose, 2 hrs post-dose 1, and 24 hrs post-dose 1 on Days 1 and 91. For the Azelastine/Fluticasone group, blood (~0.75 mL/sample on Day 1 and ~0.5 mL/sample on Day 91) was collected from CO_2-anesthetized animals (3/sex/group) via retroorbital puncture at pre-dose and 1, 2, 4, 8, and 24 hrs post-dose 1 on Days 1 and 91. For the Astelin and Fluticasone Propionate groups, blood (~0.5 mL/sample) was collected from CO_2-anesthetized animals (3/sex/group) via retroorbital puncture at pre-dose and 1, 2, 4, 8, and 24 hrs post-dose 1 on Days 1 and 91. TK animals were sacrificed by CO_2-asphyxiation following the final blood collection. Plasma levels of azelastine and fluticasone were determined by LC-MS/MS with LLOQs of 20 pg/mL and 0.5 ng/mL, respectively. The following TK parameters were calculated for azelastine: AUC, T_{max}, C_{max}, $T_{1/2}$, C_{last}, T_{last}, and (lambda)z. No TK parameters were calculated for fluticasone, as fluticasone was not detected in plasma in any treatment group.

Table 4: Mean azelastine TK parameters after intranasal administration of azelastine/fluticasone nasal spray and Astelin in male and female rats on Day 1

Parameter	Azelastine/Fluticasone		Astelin	
	Males	Females	Males	Females
T_{max} (hr)	1.00	1.00	1.00	1.00
C_{max} (pg/mL)	3330	4110	8120	7440
AUC_{0-8} (hr*pg/mL)	12130	14630	25730	24780
AUC_{last} (hr*pg/mL)	27110	35310	62600	50030
AUC_{inf} (hr*pg/mL)	27530	35840	63360	50270
AUC_{Extrap} (%)	1.53	1.47	1.20	0.49
λ_z (1/hr)	0.1523	0.1502	0.1573	0.2021
$T_{1/2}$ (hr)	4.55	4.61	4.41	3.43
T_{last} (hr)	24.00	24.00	24.00	24.00
C_{last} (pg/mL)	64.0	79.2	119	49.9

Table 5: Mean azelastine TK parameters after intranasal administration of azelastine/fluticasone nasal spray and Astelin in male and female rats on Day 91

Parameter	Azelastine/Fluticasone		Astelin	
	Males	Females	Males	Females
T_{max} (hr)	1.00	8.00	1.00	2.00
C_{max} (pg/mL)	2000	2890	3340	4640
AUC_{0-8} (hr*pg/mL)	11890	16370	14230	25630
AUC_{last} (hr*pg/mL)	27160	41240	32620	54460
AUC_{inf} (hr*pg/mL)	28340	-	33340	55330
AUC_{Extrap} (%)	4.17	-	2.16	1.57
λz (1/hr)	0.1128	-	0.1376	0.1612
$T_{1/2}$ (hr)	6.14	-	5.04	4.30
T_{last} (hr)	24.00	24.00	24.00	24.00
C_{last} (pg/mL)	133	219	99.0	140

- Parameters could not be determined for females due to a non-determinable λ_z.

On Day 1, azelastine C_{max} for both males and females in azelastine/fluticasone and Astelin groups was 1 hr. Systemic exposures (C_{max} and AUC) in the azelastine/fluticasone group were approximately half the value of the Astelin group, and there were no gender differences in exposure within groups. $T_{1/2}$ values for both treatment groups were comparable, ranging from 3.43-4.61 hrs. On Day 91, azelastine Cmax was greater for females (8 hrs) than males (1 hr) in the azelastine/fluticasone group, but similar in females (2 hrs) and males (1 hr) in the Astelin group. Systemic exposures (C_{max} and AUC) were slightly lower in males than females in both treatment groups, and systemic exposures were slightly lower in the azelastine/fluticasone group than in the Astelin group. $T_{1/2}$ values were comparable, ranging from 4.3-6.14 hrs. Finally, there was no evidence of azelastine accumulation in either treatment group from Days 1-91.

Stability and Homogeneity

Results of formulation analyses for dose concentration and stability of azelastine and fluticasone propionate were within the accepted criteria.

11 Integrated Summary and Safety Evaluation

Meda Pharmaceuticals is studying azelastine/fluticasone combination nasal spray for the treatment of allergic rhinitis in children and adults 12 years of age and older. Astelin (azelastine hydrochloride), an H_1-receptor antagonist, was approved in the US on November 1, 1996 under NDA 20-114. Flonase (fluticasone propionate), a synthetic corticosteroid, was approved in the US on October 19, 1994 US under NDA 20-121. The recommended dose of Astelin is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 years of age (Astelin approved label, April 2007), and the recommended dose of Flonase is either two 50 µg sprays in each nostril once daily, one 50 µg spray in each nostril twice daily (adults), or one 50 µg spray in each nostril once daily (starting dose in pediatric patients 4 years of age and older; Flonase approved label, March 2004).

The pharmacological and toxicological profile of the individual drug products has been well characterized. Azelastine hydrochloride showed no genotoxic effects in the Ames test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test, or chromosomal aberration test in rat bone marrow. In 2 year carcinogenicity studies in rats and mice, azelastine hydrochloride did not show evidence of carcinogenicity at oral doses up to 30 mg/kg and 25 mg/kg, respectively. Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses up to 30 mg/kg. At 68.6 mg/kg (approximately 560 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis), the duration of estrous cycles was prolonged and copulatory activity and the number of pregnancies were decreased. The numbers of corpora lutea and implantations were decreased; however, pre-implantation loss was not increased (Astelin approved label, April 2007).

Azelastine hydrochloride has been shown to cause developmental toxicity. Treatment of mice with an oral dose of 68.6 mg/kg caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification and decreased fetal weight. This dose also caused maternal toxicity as evidenced by decreased body weight. Neither fetal nor maternal effects occurred at a dose of 3 mg/kg (approximately 10 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis). In rats, an oral dose of 30 mg/kg caused malformations (oligo-and brachydactylia), delayed ossification and skeletal variations, in the absence of maternal toxicity. At 68.6 mg/kg (approximately 560 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis) azelastine hydrochloride also caused embryo-fetal death and decreased fetal weight; however, the 68.6 mg/kg dose caused severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose of 3 mg/kg (approximately 25 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis). In rabbits, oral doses of 30 mg/kg and greater (approximately 500 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis) caused abortion, delayed ossification and decreased fetal weight; however, these doses also resulted in severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose of 0.3 mg/kg (approximately 5 times the maximum recommended daily intranasal dose in adults on a mg/m^2 basis). Azelastine hydrochloride is classified as a Pregnancy Category C drug (Astelin approved label, April 2007).

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test. In carcinogenicity studies, fluticasone propionate did not show evidence of carcinogenicity at oral doses up to 1000 µg/kg in mice for 78 weeks or at inhalation doses up to 57 µg/kg in rats for 104 weeks. Reproductive studies in male and female rats revealed no impairment of fertility at subcutaneous doses up to 50 µg/kg. Prostate weight was significantly reduced at a subcutaneous dose of 50 µg/kg. Subcutaneous studies in the mouse and rat at 45 and 100 µg/kg, respectively, revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification. In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 µg/kg. However, no teratogenic effects were reported at oral doses up to 300 µg/kg in the rabbit. No fluticasome propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration. Fluticasone propionate crossed the placenta following oral administration of 100 µg/kg to rats or 300 µg/kg to rabbits. Fluticasone propionate is classified as a Pregnancy Category C drug (Flonase approved label, March 2004).

Toxicology studies (up to 14-days duration in rats and dogs) have been conducted with azelastine/fluticasone nasal spray under IND 77,363. The NOAEL for both the rat and the dog was the only combination dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day). There was no difference between species sensitivity to the drug combination in the 14-day studies, but the reviewer notes that the sponsor did not push the doses of azelastine and fluticasone in the dog. The intranasal safety margin for the sponsor's proposed clinical dose of 0.548 mg azelastine and 0.200 mg fluticasone was 0.6 (calculated using nasal surface areas of 221 cm^2 and 180 cm^2 for the dog and human, respectively).

In the current submission, the sponsor conducted a 3-month intranasal toxicity study to compare the azelastine/fluticasone combination nasal spray with the Astelin (azelastine) and fluticasone propionate marketed monoproducts. Only one dose of the azelastine/fluticasone combination (0.1% azelastine and 0.0365% fluticasone propionate; 0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day) was tested, and control (0.9% sodium chloride) and placebo (vehicle) groups were also included. Azelastine systemic exposure in the combination azelastine/fluticasone treatment group was lower than the Astelin group for males and females on Days 1 and 91. Fluticasone propionate was not detected in the plasma of the combination treatment group or the fluticasone propionate monoproduct group. Body weight was decreased in males and females in the azelastine/fluticasone (-7 and -9% for males and females, respectively) and fluticasone propionate (-6 and -15% for males and females, respectively) groups on Day 91 versus controls. Body weight gain was also decreased in males and females in the azelastine/fluticasone (-10 and -17% for males and females, respectively) and fluticasone propionate (-9 and -29% for males and females, respectively) groups (Days 1-91) versus controls. Mast cells were increased in the

mesenteric lymph nodes in the azelastine/fluticasone (9/10 males and 10/10 females) and fluticasone propionate (7/10 males and 8/10 females) groups versus controls. This increase was attributed to effects of fluticasone propionate. The sponsor considered that a portion of the intranasally administered test article may have been swallowed, resulting in this local effect in the gastrointestinal system. The sponsor also provided the following information in regards to mast cells:

> "Mast cells are often observed scattered within lymph nodes… In the experience of the Study Pathologist, an increase of mast cells is not a common result following corticosteroid administration, or at least, it is not a commonly recognized finding. Mast cells are easily identified because of their abundant cytoplasmic granules. These granules contain histamine and many other compounds. However, mast cells are not always readily identified in hematoxylin an eosin stained sections such as those evaluated in this study. Even in this study, the staining of mast cells varied among the slides reviewed and it is likely that there could be significant differences between the staining intensity of mast cells between various histology laboratories depending on the particular hematoxylin and eosin techniques used. The increased mast cells in the mesenteric lymph nodes would not be expected to have any adverse effects on the study animals."

Mast cells were also clearly increased in the mandibular lymph nodes of males (5/10) and females (5/10) in the azelastine/fluticasone group only versus control (1/10 males, 2/10 females), vehicle (2/10 males and 2/10 females), and monoproduct groups (2/10 males and 2/10 females in the Astelin group; 2/10 males and 1/10 females in the fluticasone propionate group). The toxicological significance of this finding is uncertain, given the information provided above regarding staining of mast cells with hematoxylin and eosin. In addition, unlike in the mesenteric lymph nodes, the increase in mast cells in the azelastine/fluticaseone group in the mandibular lymph nodes cannot be attributed to fluticisone, as mast cells were not increased above background in the fluticasone propionate group. Increased mast cells were also present in the tracheobronchial lymph nodes in males and females; however, the finding was not considered to be treatment-related because the incidence in control males (4/10) equaled the incidence in azelastine/fluticasone males (4/10) and females (4/10).

The NOAEL was determined to be the only dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day). Increased mast cells in the mandibular lymph node in the azelastine/fluticasone combination group versus control and monoproduct groups are of uncertain toxicological relevance as they were also found at high background levels in the tracheobronchial lymph nodes of control males. The safety margins for the sponsor's proposed clinical combination dose of 0.548 mg azelastine and 0.200 mg fluticasone propionate, based on intranasal dose, are 10 for both azelastine and fluticasone in the 3-month rat intranasal toxicity study.

Table 6: Safety margins for proposed clinical doses of azelastine and fluticasone

Maximum Daily Dose (mg)	Intranasal Dose (mg/cm^2)	Intranasal Safety Margin
Human: Azelastine: 0.548 mg Fluticasone: 0.200 mg	 Azelastine: 0.0030 Fluticasone: 0.0011	 - -
Rat 3-month toxicity study: Azelastine: 0.4 mg Fluticasone: 0.146 mg	 Azelastine: 0.031 Fluticasone: 0.011	 Azelastine: 10 Fluticasone: 10

Rat and human nasal surface areas used to calculate intranasal doses were 13 cm^2 and 180 cm^2, respectively.

APPENDIX 4

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	77,363
Supporting document/s:	SDN42
Sponsor's letter date:	January 20, 2011
CDER stamp date:	January 21, 2011
Product:	Azelastine/Fluticasone Nasal Spray
Indication:	Allergic rhinitis in adults and children 12 years of age and older
Sponsor:	Meda Pharmaceuticals, Inc. 265 Davidson Ave, Suite 300 Somerset, NJ 08873-4120
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Marcie L. Wood, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D., DABT
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Philantha Bowen

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Meda Pharmaceuticals is developing azelastine/fluticasone combination nasal spray for the treatment of allergic rhinitis in children and adults 12 years of age and older.

1.2 Brief Discussion of Nonclinical Findings

In support of the sponsor's clinical development program, 14-day repeat-dose intranasal toxicity studies in rats and dogs, as well as a pivotal 3-month intranasal toxicity study in rats with the azelastine/fluticasone combination have been completed (see nonclinical reviews by Dr. Jean Wu of the 14-day studies and Dr. Marcie Wood of the 3-month study for complete details).

In the current submission (SDN42), the sponsor submitted results of histopathological examination of additional tissues from the 3-month intranasal toxicity study in rats with the azelastine/fluticasone combination in response to a Division request to examine a complete battery of tissues in order to complete the characterization of microscopic effects of the azelastine/fluticasone combination in the rat.

No notable test article-related histopathology findings were observed in any of the tissues examined.

The NOAEL remains the only dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day).

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: No clinical protocols were included in this submission (SDN42)

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 79307-93-0 / 87474-14-2

Generic Name: Azelastine Hydrochloride/Fluticasone Propionate Nasal Spray

Code Name: MP29-02

Chemical Name:

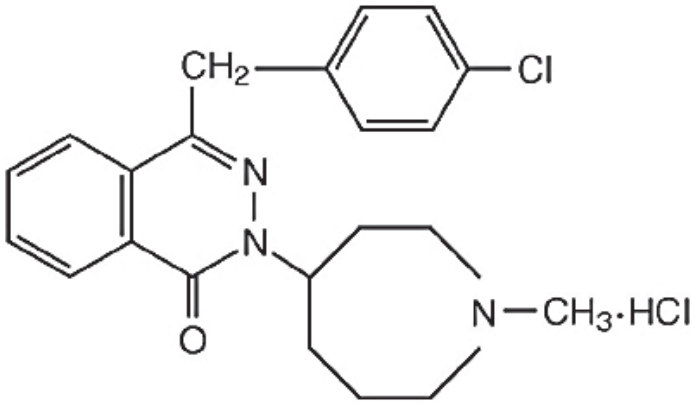
Azelastine Hydrochloride: 4-(4-Chloro-benzyl)-2-(1-methyl-azepan-4-yl)-3,4-dihydro-2H-phthal-azin-1-one Hydrochloride
Fluticasone Propionate: S-(fluoromethyl)6alpha,9-difluoro-11beta-17-dihydroxy-16alpha-methyl-3-oxoandrosta-1,4-diene-17beta-carbothioate,17-propionate

Molecular Formula/Molecular Weight

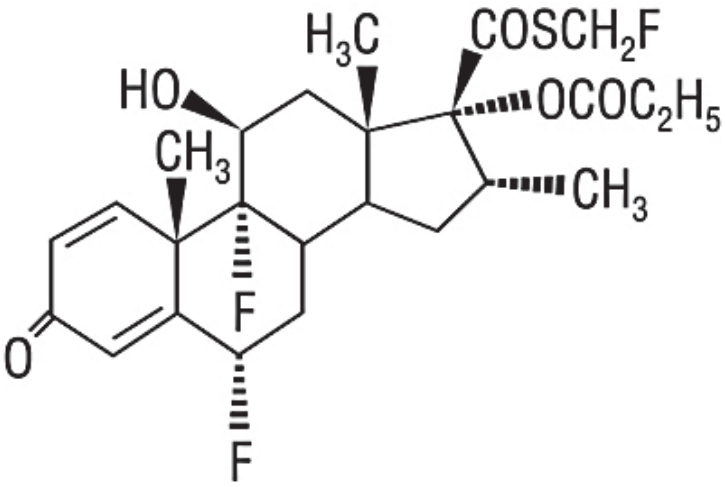
Azelastine Hydrochloride: $C_{22}H_{24}ClN_3O \cdot HCl$ / 418.37
Fluticasone Propionate: $C_{25}H_{31}F_3O_5S$ / 500.6

Structure or Biochemical Description

Azelastine Hydrochloride



Fluticasone Propionate:



Pharmacologic Class

Azelastine Hydrochloride: H_1-receptor antagonist
Fluticasone Propionate: corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

Astelin (NDA 20-114), Flonase (NDA 20-121)

2.3 Drug Formulation

Not applicable. No clinical protocols were included in this submission.

2.4 Comments on Novel Excipients

Not applicable

2.5 Comments on Impurities/Degradants of Concern

Not applicable

2.6 Proposed Clinical Protocol

No clinical protocols were included in this submission (SDN42)

2.7 Previous Clinical Experience

Astelin was approved on November 1, 1996 and Flonase was approved on October 19, 1994 in the US under NDA 20-114 and NDA 20-121, respectively. The recommended dose of Astelin is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 years of age (Astelin approved label, April 2007), and the recommended dose of Flonase is either two 50 µg sprays in each nostril once daily or one 50 µg spray in each nostril twice daily (starting dose in pediatric patients 4 years of age and older; Flonase approved label, March 2004). The fixed-dose combination product (MP29-01), Duonase Nasal Spray, was approved in India in August 2004.

Previous clinical experience with MP29-02 under IND 77,363 includes single and multiple dose clinical studies.

2.8 Regulatory Background

Meda Pharmaceuticals is developing azelastine/fluticasone combination nasal spray for the treatment of allergic rhinitis in children and adults 12 years of age and older. Pivotal 14-day repeat-dose intranasal toxicity studies in rats and dogs, as well as a pivotal 3-month intranasal toxicity study in rats with the azelastine/fluticasone combination have been completed and reviewed (see nonclinical reviews by Dr. Jean Wu of the 14-day studies and Dr. Marcie Wood of the 3-month study for complete details).

The following information request was sent to the sponsor on September 22, 2011 after completion of the review of the 3-month rat toxicology study due to an incomplete histopathological examination:

Histopathological examination was conducted on only a partial battery of tissues in the rat 3-month intranasal toxicity study (0470RM57.001). Provide results of microscopic examination of the following tissues for all treatment groups in order to fully characterize the microscopic effects of the azelastine and fluticasone combination in rats: Aorta, brain, cervix, epididymides, esophagus, eye/optic nerve, fallopian tube, gall bladder, heart, kidneys, large intestines, ovaries, pancreas, prostate, salivary gland, seminal vesicles, small intestines, stomach, testes, urinary bladder, uterus, and vagina.

The sponsor complied with the request and submitted an amendment to the 3-month rat toxicology study on January 21, 2011 (SDN42). In this review, a detailed evaluation of the completed histopathology data from Amendment 1 to the 3-month intranasal toxicity study in rats is provided.

3 Studies Submitted

3.1 Studies Reviewed

Amendment 1 to study report no. 0470RM57.001, "A 90-day intranasal toxicity study with azelastine and fluticasone in Sprague-Dawley Rats."

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Nonclinical reviews by Dr. Jean Wu for IND 77,363 dated May 1, 2007 and July 2, 2008.
Nonclinical review by Dr. Marcie Wood for IND 77,363 dated August 10, 2010.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A 90-day intranasal toxicity study with azelastine and fluticasone in Sprague-Dawley rats

Study no.:	0470RM57.001
Study report location:	SDN35, volumes C1-5
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 8, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Azelastine/Fluticasone, Lot # G70454, mean content of azelastine hydrochloride = 99% of label claim, mean content of fluticasone propionate = 102% of label claim; Fluticasone Propionate Nasal Spray, Lot/Batch # 857415A/756855A, no CoA provided in report; Astelin Nasal Spray, Lot # 0000004307, mean content of azelastine hydrochloride = 98.2% of label claim

Key Study Findings

- No notable test article-related histopathology findings were observed in any of the tissues examined.
- The NOAEL remains the only dose tested, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day).

Methods

Doses:	Control (0.9% sodium chloride), vehicle (placebo of test article), Azelastine/Fluticasone (0.4 mg azelastine/day and 0.146 mg fluticasone/day, Astelin, and Fluticasone Propionate
Frequency of dosing:	Twice daily for 91 days
Route of administration:	Intranasal
Dose volume:	0.1 mL/nostril at each dosing session = 0.4 mL/day
Formulation/Vehicle:	Placebo of test article
Species/Strain:	Sprague Dawley rat (Crl:CD(SD))
Number/Sex/Group:	10/sex/group for the main toxicology study
Age:	Approximately 6.5 weeks old at initiation of dosing
Weight:	Males: 171-224 g; Females: 129-181 g (Day 1 study weights)
Satellite groups:	The following animals were assigned for toxicokinetics: 3/sex for control and vehicle groups, 9/sex for the Azelastine/Fluticasone group, and 6/sex for the Astelin and Fluticasone Propionate groups. A recovery group was not included.
Unique study design:	None
Deviation from study protocol:	Only minor deviations occurred

Observations and Results

Histopathology

Adequate Battery

The following additional tissues were processed in paraffin, sectioned, and stained with hematoxylin and eosin: aorta, brain, cervix, epididymides, esophagus, eye/optic nerve, fallopian tube, heart, kidneys, large intestines, ovaries, pancreas, prostate, salivary gland, seminal vesicles, small intestines, stomach, testes, urinary bladder, uterus, and vagina.

Peer Review

A peer review was not performed.

Histological Findings

No notable test article-related histopathology findings were observed in any of the tissues examined.

11 Integrated Summary and Safety Evaluation

Meda Pharmaceuticals is studying azelastine/fluticasone combination nasal spray for the treatment of allergic rhinitis in children and adults 12 years of age and older. Astelin (azelastine hydrochloride), an H_1-receptor antagonist, was approved in the US on November 1, 1996 under NDA 20-114. Flonase (fluticasone propionate), a synthetic corticosteroid, was approved in the US on October 19, 1994 US under NDA 20-121. The recommended dose of Astelin is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 years of age (Astelin approved label, April 2007), and the recommended dose of Flonase is either two 50 µg sprays in each nostril once daily, one 50 µg spray in each nostril twice daily (adults), or one 50 µg spray in each nostril once daily (starting dose in pediatric patients 4 years of age and older; Flonase approved label, March 2004).

In support of the sponsor's clinical development program, 14-day repeat-dose intranasal toxicity studies in rats and dogs, as well as a pivotal 3-month intranasal toxicity study in rats with the azelastine/fluticasone combination have been completed (see nonclinical reviews by Dr. Jean Wu of the 14-day studies and Dr. Marcie Wood of the 3-month study for complete details).

In the current submission (SDN42), the sponsor submitted results of histopathological examination of additional tissues from the 3-month intranasal toxicity study in rats with the azelastine/fluticasone combination in response to a Division request to examine a complete battery of tissues in order to complete the characterization of microscopic effects of the azelastine/fluticasone combination in the rat.

No notable test article-related histopathology findings were observed in any of the tissues examined.

The NOAEL remains the only combination dose tested in the 3-month rat toxicity study, 0.1% azelastine and 0.0365% fluticasone propionate (0.4 mL/day = 0.4 mg azelastine/day and 0.146 mg fluticasone/day).

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/s/

MARCIE L WOOD
09/23/2011

TIMOTHY W ROBISON
09/23/2011
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA CHEMISTRY CONSULT

Application number:	NDA 202236
Supporting document/s:	SDN1
Applicant's letter date:	April 1, 2011
CDER stamp date:	April 1, 2011
Product:	Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.37% Nasal Spray
Indication:	Seasonal allergic rhinitis
Applicant:	Meda Pharmaceuticals, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Marcie Wood, Ph.D.
Supervisor/Team Leader:	Timothy Robison, Ph.D. DABT
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Philantha Bowen

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202236 are owned by Meda Pharmaceuticals, Inc. or are data for which Meda Pharmaceuticals, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 202236 that Meda Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 202236.

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1 Executive Summary

1.1 Introduction

The review chemist, Dr. Eugenia Nashed, requested a safety assessment of the observed leachables greater than the limit of quantitation in the drug product, azelastine hydrochloride 0.1% and fluticasone propionate 0.37% nasal spray.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): N/A

Generic Name: Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.37% Nasal Spray

Code Name: MP29-02

Chemical Name

Azelastine Hydrochloride: (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-,monohydrochloride

Fluticasone Propionate: S-(fluoromethyl) 6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate

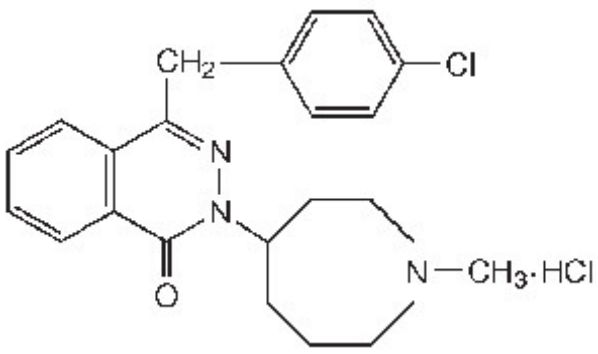
Molecular Formula/Molecular Weight

Azelastine Hydrochloride: $C_{22}H_{24}ClN_3O \bullet HCl$ / 418.37

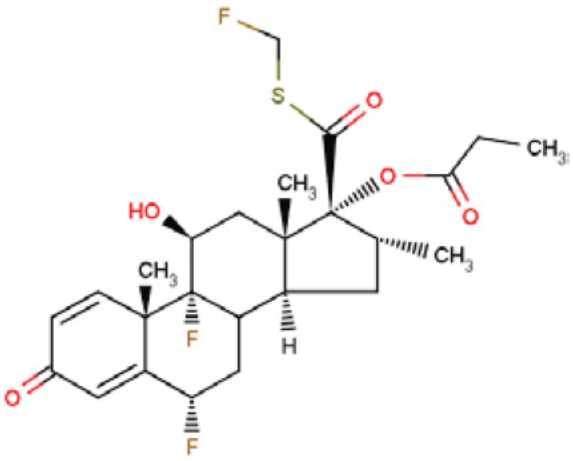
Fluticasone Propionate: $C_{25}H_{31}F_3O_5S$ / 500.6

Structure or Biochemical Description

Azelastine Hydrochloride:



Fluticasone Propionate:



Pharmacologic Class

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 77,363 (Meda Pharmaceuticals, Inc., Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.37% Nasal Spray)
NDA 20-114 (Meda Pharmaceuticals, Inc., Astelin (Azelastine Hydrochloride) Nasal Spray)
NDA 20-121 (GlaxoSmithKline, Flonase (Fluticasone Propionate) Nasal Spray)
DMFs (b) (4)
multidose nasal spray pump (b) (4)
actuator and cap)
DMF (b) (4) Type 1 amber glass bottles (b) (4)

2.3 Drug Formulation

The drug product contains azelastine hydrochloride and fluticasone propionate in a suspension with the following excipients.

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

(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

The amounts of observed leachables greater than the limit of quantitation in the drug product are acceptable. As the sponsor has proposed a specification limit of (b) (4) for the observed leachables, the maximum daily exposure for each leachable will not exceed (b) (4) (based on 137 mg drug product /spray, 4 sprays/day for a total amount of 548 mg drug product/day).

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication for MP29-02 is for the relief of the symptoms of seasonal allergic rhinitis in patients 12 years of age and older. The recommended dose is one spray per nostril twice daily (137 µg of azelastine hydrochloride and 50 µg fluticasone propionate per spray) for a total daily dose of 548 µg of azelastine hydrochloride and 200 µg of fluticasone propionate.

2.7 Regulatory Background

The two active principal ingredients, azelastine and fluticasone propionate, in the proposed fixed dose combination product, are approved monoproducts. Astelin was approved on November 1, 1996 and Flonase was approved on October 19, 1994 in the US under NDA 20-114 and NDA 20-121, respectively. The recommended dose of Astelin is one or two 137 µg sprays per nostril twice daily for adults and children ≥ 12 years of age (Astelin approved label, April 2007), and the recommended dose of Flonase is either two 50 µg sprays in each nostril once daily or one 50 µg spray in each nostril twice daily (starting dose in pediatric patients 4 years of age and older; Flonase approved label, March 2004).

11 Integrated Summary and Safety Evaluation

The review chemist, Dr. Eugenia Nashed, requested a safety assessment of the observed leachables greater than the limit of quantitation in the drug product, summarized in the table below (excerpted from the sponsor's submission).

Table 3: Summary of Observed Leachables Greater Than LOQ

Batch No./ Orientation	Stability Test Interval	Storage Condition	Observed Leachable	Concentration (ppm)
G70729 / Horizontal	12 Months	25°C/60% RH	(b) (4)	
G70730 / Upright	12 Months	25°C/60% RH		
G70730 / Horizontal	12 Months	25°C/60% RH		
G70730 / Horizontal	12 Months	25°C/60% RH		
G70731 / Upright	12 Months	25°C/60% RH		
G70731 / Upright	12 Months	25°C/60% RH		
G70731 / Horizontal	12 Months	25°C/60% RH		
G70731 / Horizontal	12 Months	25°C/60% RH		
G70453 / Upright	12 Months	25°C/60% RH		
G70729 / Upright	36 Months	25°C/60% RH		
G70730 / Horizontal	36 Months	25°C/60% RH		

The sponsor has proposed a specification limit of (b) (4) for the observed leachables; therefore, the maximum daily exposure for each leachable will not exceed (b) (4) (based on 137 mg drug product/spray, 4 sprays/day for a total amount of 548 mg drug product/day). (b) (4) pose no safety concern, as the maximum daily exposures for each leachable are below 5 µg/day, the qualification threshold for leachables with negligible safety concerns for non-carcinogenic effects, recommended by the Product Quality Research Institute Working Group. (b) (4) also poses no safety concern as the maximum daily exposure is below the acceptable daily exposure level (calculated from the TWA for (b) (4) with additional safety factors applied, see below).

(b) (4)

(b) (4)

Recommendation:
The proposed levels and specifications for all of the above leachables are acceptable.

12 Appendix/Attachments

1. Email from chemistry reviewer Dr. Jean Nashed, dated August 5, 2011, requesting a safety assessment of leachables.

APPENDIX 1

From: Nashed, Eugenia M
Sent: Friday, August 05, 2011 2:20 PM
To: Wood, Marcie L; Robison, Timothy W
Cc: Schroeder, Alan C; Peri, Prasad
Subject: N 202-236 Dymista NS Leachables Consult to PharmTox

Attachments: Picture (Device Independent Bitmap)
Hello Marcie and Tim,

See below the list of leachables observed above the LOQ in the combination drug product on stability.
Please evaluate. Thank you … Jean

PS: If you need additional information or data please let us know. I will be on vacation starting tomorrow, but Alan is coming back on Mon.

Table 3: Summary of Observed Leachables Greater Than LOQ

Batch No./ Orientation	Stability Test Interval	Storage Condition	Observed Leachable	Concentration (ppm)
G70729 / Horizontal	12 Months	25°C/60% RH	(b) (4)	
G70730 / Upright	12 Months	25°C/60% RH		
G70730 / Horizontal	12 Months	25°C/60% RH		
G70730 / Horizontal	12 Months	25°C/60% RH		
G70731 / Upright	12 Months	25°C/60% RH		
G70731 / Upright	12 Months	25°C/60% RH		
G70731 / Horizontal	12 Months	25°C/60% RH		
G70731 / Horizontal	12 Months	25°C/60% RH		
G70453 / Upright	12 Months	25°C/60% RH		
G70729 / Upright	36 Months	25°C/60% RH		
G70730 / Horizontal	36 Months	25°C/60% RH		

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/s/

MARCIE L WOOD
09/23/2011

TIMOTHY W ROBISON
09/23/2011
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202236 **Applicant: MEDA Pharmaceuticals, Inc.** **Stamp Date: 4/01/2011**

Drug Name: Azelastine Hydrochloride 0.1% and Fluticasone Propionate 0.037% Nasal Spray **NDA/BLA Type: Original - Standard**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The proposed labeling is in the PLR format. Changes in text will be handled in the labeling review.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Marcie Wood, Ph.D — May 13, 2011
Reviewing Pharmacologist — Date

Timothy Robison, Ph.D, DABT — May 13, 2011
Team Leader/Supervisor — Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

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MARCIE L WOOD
05/13/2011

TIMOTHY W ROBISON
05/13/2011
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