HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DYMISTA™ Nasal Spray safely and effectively. See full prescribing information for DYMISTA Nasal Spray.
DYMISTA (azelastine hydrochloride and fluticasone propionate) Nasal Spray

Initial U.S. Approval: 2012

INDICATIONS AND USAGE

Dymista Nasal Spray, containing an H_1-receptor antagonist and a corticosteroid, is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief. (1.1)

DOSAGE AND ADMINISTRATION

- For intranasal use only. (2.1)
- Recommended dose is 1 spray per nostril twice daily in adults and adolescents 12 years of age and older (2.1)
- Prime before initial use and when it has not been used for 14 or more days. (2.2)

DOSAGE FORMS AND STRENGTHS

Dymista Nasal Spray: 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate (137 mcg/50 mcg) in each 0.137 mL spray. (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Somnolence: Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking Dymista Nasal Spray. (5.1)
- Avoid concurrent use of alcohol or other central nervous system (CNS) depressants with Dymista Nasal Spray because further decreased alertness and impairment of CNS performance may occur. (5.1)
- Epistaxis, nasal ulcerations, nasal septal perforation, impaired wound healing, *Candida albicans* infection. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma. (5.2)
- Development of glaucoma or posterior subcapsular cataracts. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts. (5.3)
- Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections. (5.4)
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue Dymista Nasal Spray slowly. (5.5)
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving Dymista Nasal Spray. (5.7, 8.4)

ADVERSE REACTIONS

The most common adverse reactions (≥2% incidence) are: dysgeusia, epistaxis, and headache. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at 1-888-939-6478 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Potent inhibitors of cytochrome P450 (CYP) 3A4: May increase blood levels of fluticasone propionate.
- Ritanovir: Coadministration is not recommended. (5.6, 7.2)
- Other potent CYP3A4 inhibitors, such as ketoconazole: use caution with coadministration. (5.6, 7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Dymista Nasal Spray is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of Dymista Nasal Spray, 137 mcg/50 mcg, is 1 spray per nostril twice daily for seasonal allergic rhinitis. Each spray contains 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate (137 mcg/50 mcg).

Administer Dymista Nasal Spray by the intranasal route only.

2.2 Important Administration Instructions

Shake the bottle gently before each use.

Priming: Prime Dymista Nasal Spray before initial use by releasing 6 sprays or until a fine mist appears. When Dymista Nasal Spray has not been used for 14 or more days, reprime with 1 spray or until a fine mist appears. Avoid spraying Dymista Nasal Spray into the eyes. If sprayed in the eyes, flush eyes with water for at least 10 minutes.

3 DOSAGE FORMS AND STRENGTHS

Dymista is a nasal spray suspension. Each spray delivers a volume of 0.137 mL suspension containing 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate (137 mcg/50 mcg).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence

In clinical trials, the occurrence of somnolence has been reported in some patients (6 of 853 patients) taking Dymista Nasal Spray [*see Adverse Reactions (6.1)*]. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor

coordination such as operating machinery or driving a motor vehicle after administration of Dymista Nasal Spray. Concurrent use of Dymista Nasal Spray with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur [*see Drug Interactions (7.1)*].

5.2 Local Nasal Effects

In clinical trials of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients treated with Dymista Nasal Spray than those who received placebo [*see Adverse Reactions (6)*].

Instances of nasal ulceration and nasal septal perforation have been reported in patients following the intranasal application of corticosteroids. There were no instances of nasal ulceration or nasal septal perforation observed in clinical trials with Dymista Nasal Spray.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use Dymista Nasal Spray until healing has occurred.

In clinical trials with fluticasone propionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with Dymista Nasal Spray. Patients using Dymista Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

5.3 Glaucoma and Cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Glaucoma and cataract formation were evaluated with intraocular pressure measurements and slit lamp examinations in a controlled 12-month study in 612 adolescent and adult patients aged 12 years and older with perennial allergic or vasomotor rhinitis (VMR). Of the 612 patients enrolled in the study, 405 were randomized to receive Dymista Nasal Spray (1 spray per nostril twice daily) and 207 were randomized to receive fluticasone propionate nasal spray (2 sprays per nostril once daily). In the Dymista Nasal Spray group, one patient had increased intraocular pressure at month 6. In addition, three patients had evidence of posterior subcapsular cataract at month 6 and one at month 12 (end of treatment). In the fluticasone propionate group, three patients had evidence of posterior subcapsular cataract at month 12 (end of treatment).

5.4 Immunosuppression

Persons who are using drugs, such as corticosteroids, that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The

contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex because of the potential for worsening of these infections.

5.5 Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects

When intranasal steroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of Dymista Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy. The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

5.6 Use of Cytochrome P450 3A4 Inhibitors

Ritonavir and other strong cytochrome P450 3A4 (CYP3A4) inhibitors can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of Dymista Nasal Spray and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Use caution with the coadministration of Dymista Nasal Spray and other potent CYP3A4 inhibitors, such as ketoconazole [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*].

5.7 Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving Dymista Nasal Spray [*see Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Somnolence [*see Warnings and Precautions (5.1)*]
- Local nasal effects, including epistaxis, nasal ulceration, nasal septal perforation, impaired wound healing, and *Candida albicans* infection [*see Warnings and Precautions (5.2)*]
- Cataracts and glaucoma [*see Warnings and Precautions (5.3)*]
- Immunosuppression [*see Warnings and Precautions (5.4)*]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [*see Warnings and Precautions (5.5 and 5.7), Use in Specific Populations (8.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

The safety data described below reflect exposure to Dymista Nasal Spray in 853 patients (12 years of age and older; 36% male and 64% female) with seasonal allergic rhinitis in 3 double-blind, placebo-controlled clinical trials of 2-week duration. The racial distribution for the 3 clinical trials was 80% white, 16% black, 2% Asian, and 1% other. In the 12-month open-label, active-controlled clinical trial, 404 Asian patients (240 males and 164 females) with perennial allergic rhinitis or vasomotor rhinitis were treated with Dymista Nasal Spray, 1 spray per nostril twice daily.

Adults and Adolescents 12 Years of Age and Older

In the 3 placebo controlled clinical trials of 2-week duration, 3411 patients with seasonal allergic rhinitis were treated with 1 spray per nostril of Dymista Nasal Spray, azelastine hydrochloride nasal spray, fluticasone propionate nasal spray, or placebo, twice daily. The azelastine hydrochloride and fluticasone propionate comparators use the same vehicle and device as Dymista Nasal Spray and are not commercially marketed. Overall, adverse reactions were 16% in the Dymista Nasal Spray treatment groups, 15% in the azelastine hydrochloride nasal spray groups, 13% in the fluticasone propionate nasal spray groups, and 12% in the placebo groups. Overall, 1% of patients in both the Dymista Nasal Spray and placebo groups discontinued due to adverse reactions.

Table 1 contains adverse reactions reported with frequencies greater than or equal to 2% and more frequently than placebo in patients treated with Dymista Nasal Spray in the seasonal allergic rhinitis controlled clinical trials.

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