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		2. Label Review Number (Biologics)		
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4. Proprietary Name DYMISTA		5. Established Name azelastine hydrochloride and fluticasone propionate Product Code No.:		
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8. Advertisement / Promotional Labeling Materials				
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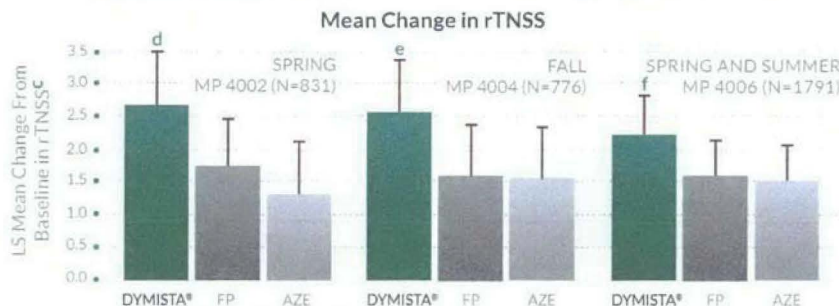
Rapid Relief^a with Significant Improvement of Nasal Symptoms

DYMISTA® (azelastine hydrochloride and fluticasone propionate) Nasal Spray Demonstrated Rapid Relief^a vs Placebo, and Significantly Greater Improvement in Total Nasal Symptoms vs Azelastine HCl or Fluticasone Propionate Comparators

^aAs demonstrated in patients 12 and older, fast relief is defined as the first timepoint (30 minutes) at which DYMISTA® was significantly superior to placebo in the mean change from baseline in instantaneous total nasal symptom score (iTNSS) and was sustained thereafter.¹

- In a pivotal trial with symptomatic adolescent and adult patients having moderate to severe SAR, the reduction in nasal symptom scores with DYMISTA® was statistically significant vs placebo within 30 minutes, and that significant difference was maintained throughout the 4-hour observation period¹
 - In a survey, 85% of patients identified rapid relief of symptoms as one of the most important attributes of SAR treatment³
- Across 3 pivotal clinical trials, involving patients 12 years of age and older, DYMISTA® provided statistically significant ($P \leq .038$) improvement in placebo-subtracted reflective Total Nasal Symptom Scores (rTNSS) ranging from 43% to 67% greater than that of azelastine HCl or fluticasone propionate, over a 14-day study period¹
 - DYMISTA® also showed consistent, statistically significant ($P < .001$) improvement in rTNSS regardless of the allergy season when compared with placebo¹

Improvement In Reflective Total Nasal Symptom Scores^b



^bThe azelastine hydrochloride and fluticasone propionate comparators used the same device and vehicle as DYMISTA and are not commercially marketed.¹

^cPlacebo-subtracted. ^d $P < .034$ vs FP; $P = .001$ vs AZE. ^e $P < .038$ vs FP; $P = .032$ vs AZE. ^f $P < .029$ vs FP; $P = .016$ vs AZE. AZE = azelastine HCl; FP = fluticasone propionate; rTNSS = reflective Total Nasal Symptom Score.

Source: DYMISTA [package insert].¹

IMPORTANT SAFETY INFORMATION

- Somnolence: Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking DYMISTA.
- Avoid concurrent use of alcohol or other central nervous system (CNS) depressants with DYMISTA because further decreased alertness and impairment of CNS performance may occur.
- 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.

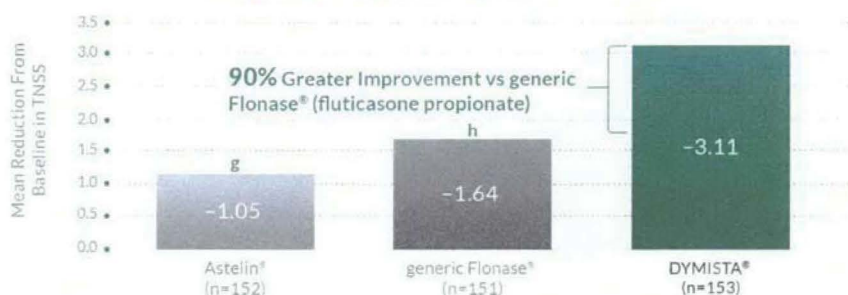
Please see Important Safety Information throughout and enclosed full Prescribing Information.

Sustained Improvement Over 2 Weeks vs Active Comparators

DYMISTA® (azelastine hydrochloride and fluticasone propionate) Nasal Spray Demonstrated Significantly Greater Improvement in Total Nasal Symptom Relief vs Astelin® and Generic Flonase® Over 2 Weeks ($P < .001$).²

- In a supportive Phase III, randomized, double-blind, parallel-group study of patients 12 years of age and older, DYMISTA® achieved 90% greater improvement in placebo-subtracted TNSS vs generic Flonase® (fluticasone propionate), which represents a 1.47 numerical difference in TNSS.^{2,4}
 - DYMISTA® was significantly different from both generic fluticasone propionate and azelastine HCl ($P < .05$).⁴

Magnitude of Nasal Symptom Relief



Change from baseline in the placebo-subtracted mean TNSS for each day (maximum score 24), averaged over the 14-day study period.² Percent difference represents the improvement in TNSS with DYMISTA® relative to commercially available generic Flonase® (fluticasone propionate) comparator.^{2,4}

^g $P < .001$ vs Astelin®; ^h $P = .003$ vs generic Flonase®.

TNSS = Total Nasal Symptoms Score.

Sources: Hampel 2010²; Data on file.⁴

- The most common adverse events in this trial for DYMISTA® were dysgeusia (7.2%), epistaxis (3.9%), and headache (2.6%).²
- Over 14 days, DYMISTA® significantly improved total nasal symptoms compared with azelastine HCl ($P \leq .01$) or placebo ($P \leq .01$) on each day of the study, while significant improvement was noted compared with fluticasone propionate nasal spray ($P < .01$) on each study day except days 10 and 11.²

IMPORTANT SAFETY INFORMATION (continued)

- 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.
- 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.
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue DYMISTA slowly.
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving DYMISTA.

Please see Important Safety Information throughout and enclosed full Prescribing Information.

Safety and Tolerability in Children, Adolescents, and Adults

Safety and Tolerability of DYMISTA® (azelastine hydrochloride and fluticasone propionate) Nasal Spray Has Been Widely Studied in >4000 Patients (Including Children, Adolescents, and Adults)

Children 6 to 11 Years of Age

- Safety results from a 2-week, double-blind, placebo-controlled clinical trial in children 6 to 11 years of age with SAR found that children treated with DYMISTA® for 2 weeks (N=302) experienced more adverse reactions than those receiving placebo: overall incidence of adverse reactions (16% vs 12%), dysgeusia (4% vs 0%), and epistaxis (4% vs 3%)¹
 - In both treatment groups, 1% of patients discontinued use due to adverse reactions
 - Somnolence was not reported
- A 3-month open-label safety trial conducted in children 6 to 11 years of age (N=353) found that more treatment-emergent adverse events occurred in children receiving combination therapy with DYMISTA® (n=264) compared to fluticasone propionate (n=89) (1 spray in each nostril twice daily)⁴
 - No nasal ulcerations or septal perforations were observed
 - 2% of patients in the DYMISTA® group and 3% in the fluticasone propionate group discontinued use because of adverse events
 - There were two reports of somnolence, one severe, among children taking DYMISTA®

Adolescents and Adults

- In adolescents and adults with SAR, the overall incidence of adverse reactions were comparable in all treatment groups (N=3411)¹

Adverse Reactions ≥2% Incidence in 2-week Seasonal Allergic Rhinitis Pivotal Trials (Studies MP 4002, MP 4004, and MP 4006)

	DYMISTA® (n=853)	azelastine HCl ¹ (n=851)	fluticasone propionate ¹ (n=846)	placebo (n=861)
Overall Incidence	16%	15%	13%	12%
Dysgeusia	4%	5%	1%	<1%
Epistaxis	2%	2%	2%	2%
Headache	2%	2%	2%	1%

The azelastine hydrochloride and fluticasone propionate comparators used the same device and vehicle as DYMISTA and are not commercially marketed.¹

Source: DYMISTA [package insert].¹

- In a separate 12-month, open-label safety trial (N=611), the overall rate of any adverse reaction was 47% with DYMISTA® and 44% with fluticasone propionate^{4,j}
 - Of patients treated with DYMISTA®: None had severe epistaxis, 2% had mild epistaxis, and <1% had moderate epistaxis. No nasal ulcerations or septal perforations were observed
 - In both treatment groups, 3% of patients discontinued use because of adverse reactions

^jAs listed in the Full Prescribing Information, this trial was an open-label, active-controlled study in which 404 patients (12 years of age and older) with chronic allergic or nonallergic vasomotor rhinitis were treated with DYMISTA® 1 spray per nostril twice daily, and 207 patients were treated with fluticasone propionate 2 sprays per nostril once daily.⁴

IMPORTANT SAFETY INFORMATION (continued)

- Potent inhibitors of cytochrome P450 (CYP) 3A4: May increase blood levels of fluticasone propionate.
- Ritanovir: Coadministration is not recommended.
- Other potent CYP3A4 inhibitors, such as ketoconazole: use caution with coadministration.
- The most common adverse reactions (≥2% incidence) are: dysgeusia, epistaxis, and headache.

Please see accompanying Brief Summary of Prescribing Information following this ad.
Please see Important Safety Information throughout and enclosed full Prescribing Information.

Important Safety Information / References

INDICATIONS

DYMISTA contains an H₁-receptor antagonist and a corticosteroid, and is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

IMPORTANT SAFETY INFORMATION

- Somnolence: Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking DYMISTA.
- Avoid concurrent use of alcohol or other central nervous system (CNS) depressants with DYMISTA because further decreased alertness and impairment of CNS performance may occur.
- 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.
- 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.
- 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.
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue DYMISTA slowly.
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving DYMISTA.
- Potent inhibitors of cytochrome P450 (CYP) 3A4: May increase blood levels of fluticasone propionate.
- Ritanovir: Coadministration is not recommended.
- Other potent CYP3A4 inhibitors, such as ketoconazole: use caution with coadministration.
- The most common adverse reactions (≥2% incidence) are: dysgeusia, epistaxis, and headache.

Please see enclosed full Prescribing Information.

REFERENCES

1. DYMISTA [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2015.
2. Hampel FC, Ratner PH, van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol.* 2010;105(2):168-173.
3. Marple BF, Formadley JA, Patel AA, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg.* 2007;136(suppl 6):S107-S124.
4. Data on file. Meda Pharmaceuticals Inc.

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DYMISTA[®]
(azelastine hydrochloride and
fluticasone propionate) Nasal Spray
137 mcg/50 mcg per Spray

US/DYM/0515/0068k

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DYMISTA (azelastine hydrochloride and fluticasone propionate) nasal spray, for intranasal use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Consult Package Insert for full prescribing information before prescribing

INDICATIONS

DYMISTA contains an H₁-receptor antagonist and a corticosteroid, and is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

WARNINGS AND PRECAUTIONS

Somnolence

In clinical trials, the occurrence of somnolence has been reported in some patients (6 of 853 adult and adolescent patients and 2 of 416 children) taking DYMISTA in controlled trials. 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. Concurrent use of DYMISTA 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.

Local Nasal Effects

In clinical trials of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients treated with DYMISTA than those who received placebo.

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. Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should avoid use of DYMISTA 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. Patients using DYMISTA over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

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 (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 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).

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.

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 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.

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. 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 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 and other potent CYP3A4 inhibitors, such as ketoconazole.

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.

ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Somnolence
- Local nasal effects, including epistaxis, nasal ulceration, nasal septal perforation, impaired wound healing, and *Candida albicans* infection
- Glaucoma and cataracts
- Immunosuppression
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction

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.

Adults and Adolescents 12 Years of Age and Older

The safety data described below in adults and adolescents 12 years of age and older reflect exposure to DYMISTA 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 3 placebo controlled clinical trials of 2-week duration, 3411 patients with seasonal allergic rhinitis were treated with 1 spray per nostril of DYMISTA, 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 and are not commercially marketed. Overall, adverse reactions were 16% in the DYMISTA 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 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 in the seasonal allergic rhinitis controlled clinical trials.

Table 1. Adverse Reactions with ≥2% Incidence and More Frequently than Placebo in Placebo-Controlled Trials of 2 Weeks Duration with DYMISTA in Adult and Adolescent Patients with Seasonal Allergic Rhinitis				
1 spray per nostril twice daily				
	DYMISTA (N=853)*	Azelastine Hydrochloride Nasal Spray† (N=851)	Fluticasone Propionate Nasal Spray† (N=846)	Vehicle Placebo (N=861)
Dysgeusia	30(4%)	44(5%)	4(1%)	2(<1%)
Headache	18(2%)	20(2%)	20(2%)	10(1%)
Epistaxis	16(2%)	14(2%)	14(2%)	15(2%)

*Safety population N=853, intent-to-treat population N=848

†Not commercially marketed

In the above trials, somnolence was reported in <1% of patients treated with DYMISTA (6 of 853) or vehicle placebo (1 of 861).

Pediatric Patients 6-11 Years of Age

The safety data described below in children 6-11 years of age reflect exposure to DYMISTA in 152 patients (6-11 years of age; 57% male and 43% female) with seasonal allergic rhinitis in one double-blind, placebo-controlled clinical trial of 2-week duration. The racial distribution for the clinical trial was 69% white, 31% black, 2% Asian, and 2% other.

In the placebo controlled clinical trial of 2-week duration, patients with seasonal allergic rhinitis were treated with 1 spray per nostril of DYMISTA or placebo, twice daily. Overall, adverse reactions were 16% in the DYMISTA treatment group, and 12% in the placebo group. Overall, 1% of patients in both the DYMISTA and placebo groups discontinued due to adverse reactions.

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

Table 2. Adverse Reactions with ≥2% Incidence and More Frequently than Placebo in Placebo-Controlled Trials of 2 Weeks Duration with DYMISTA in Children 6 to 11 Years of Age with Seasonal Allergic Rhinitis		
1 spray per nostril twice daily		
	DYMISTA (N=152)*	Vehicle Placebo (N=152)
Dysgeusia	6 (4%)	0 (0%)
Epistaxis	6 (4%)	4 (3%)

*Safety population N=152, intent-to-treat population N=152

In the above trial, somnolence was not reported.

Long-Term (12 Month) Safety Trial in Adults and Adolescents 12 Years of Age and Older:

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, 1 spray per nostril twice daily.

In the 12-month, open-label, active-controlled, long-term safety trial in adults and adolescents 12 years of age and older, 404 patients with perennial allergic rhinitis or vasomotor rhinitis were treated with DYMISTA 1 spray per nostril twice daily and 207 patients were treated with fluticasone propionate nasal spray, 2 sprays per nostril once daily. Overall, adverse reactions were 47% in the DYMISTA treatment group and 44% in the fluticasone propionate nasal spray group. The most frequently reported adverse reactions (≥2%) with DYMISTA were headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhea, and epistaxis. In the DYMISTA treatment group, 7 patients (2%) had mild epistaxis and 1 patient (<1%) had moderate epistaxis. In the fluticasone propionate nasal spray treatment group 1 patient (<1%) had mild epistaxis. No patients had reports of severe epistaxis. Focused nasal examinations were performed and no nasal ulcerations or septal perforations were observed. Eleven of 404 patients (3%) treated with DYMISTA and 6 of 207 patients (3%) treated with fluticasone propionate nasal spray discontinued from the trial due to adverse events.

Long-Term (3-Month) Safety Trial in Pediatric Patients 6-11 Years of Age

In the 3-month open label, active-controlled, clinical trial, 264 patients (60% male, 40% female) (80% white, 19% black, 4% Asian and 2% other) with allergic rhinitis were treated with DYMISTA, 1 spray per nostril twice daily.

In the 3-month, open label, active-controlled, safety trial in pediatric patients 6-11 years of age 264 patients (128 patients ≥6 to <9 years of age, and 136 patients ≥9 to <12 years of age) with allergic rhinitis (based on the Investigator's assessment) were treated with DYMISTA, 1 spray per nostril twice daily and 89 patients (44 patients ≥6 to <9 years of age, and 45 patients ≥9 to <12 years of age) were treated with fluticasone propionate nasal spray, 1 spray per nostril twice daily. Overall, adverse

reactions were 40% in the DYMISTA treatment group and 36% in the fluticasone propionate nasal spray group. The most frequently reported adverse reactions ($\geq 2\%$) with DYMISTA were epistaxis, headache, oropharyngeal pain, vomiting, upper abdominal pain, cough, pyrexia, otitis media, upper respiratory tract infection, diarrhea, nausea, otitis externa, and urticaria. In the DYMISTA treatment group 23 patients (9%) had mild epistaxis and 3 patients (1%) had moderate epistaxis. In the fluticasone propionate nasal spray treatment group 8 patients (9%) had mild epistaxis. No patients had reports of severe epistaxis. Focused nasal examinations were performed and no ulcerations or septal perforations were observed. Four of 264 patients (2%) treated with DYMISTA and 3 of 89 (3%) treated with fluticasone propionate nasal spray discontinued from the trial due to adverse events. There were two reports of somnolence, one severe, among children taking DYMISTA.

Postmarketing Experience

The following spontaneous adverse events have been reported with DYMISTA or one of the components (azelastine and fluticasone). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: atrial fibrillation, increased heart rate, palpitations

Eye disorder: blurred vision, cataracts, conjunctivitis, dryness and irritation, eye swelling, glaucoma, increased intraocular pressure, vision abnormal, xerophthalmia

Gastrointestinal disorders: nausea, vomiting

General disorders and administration site condition: aches and pain, application site irritation, chest pain, edema of face and tongue, fatigue, tolerance

Immune system disorders: anaphylaxis/anaphylactoid reactions which in rare instances were severe, hypersensitivity reactions

Musculoskeletal and connective tissue disorders: growth suppression

Nervous system disorders: disturbance or loss of smell and/or taste, dizziness, involuntary muscle contractions, paresthesia, parosmia

Psychiatric disorders: anxiety, confusion, nervousness

Renal and urinary disorders: urinary retention

Respiratory, thoracic and mediastinal disorders: bronchospasm, cough, dysphonia, dyspnea, hoarseness, nasal septal perforation, nasal discomfort, nasal dryness, nasal sores, nasal ulcer, sore throat, throat dryness and irritation, voice changes, wheezing

Skin and subcutaneous tissue disorder: angioedema, erythema, face swelling, pruritus, rash, urticaria

Vascular disorder: hypertension

DRUG INTERACTIONS

No formal drug interaction studies have been performed with DYMISTA. The drug interactions of the combination are expected to reflect those of the individual components.

Central Nervous System Depressants

Concurrent use of DYMISTA with alcohol or other central nervous system depressants should be avoided because somnolence and impairment of central nervous system performance may occur.

Cytochrome P450 3A4

Ritonavir (a strong CYP3A4 inhibitor) significantly increased plasma fluticasone propionate exposure following administration of fluticasone propionate aqueous nasal spray, resulting in significantly reduced serum cortisol concentrations. 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 fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Ketoconazole (also a strong CYP3A4 inhibitor), administered in multiple 200 mg doses to steady-state, increased plasma exposure of fluticasone propionate, reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol, following administration of a single 1000 mcg dose of fluticasone propionate by oral inhalation route.

Caution should be exercised when DYMISTA is coadministered with ketoconazole and other known strong CYP3A4 inhibitors.

USE IN SPECIFIC POPULATIONS

Pregnancy

DYMISTA: Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled clinical trials of DYMISTA, azelastine hydrochloride only, or fluticasone propionate only in pregnant women. Animal reproductive 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/m² 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/m² 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/m² basis at a maternal dose of 30 mg/kg). At a dose approximately 1200 times the MRHDID (on a mg/m² 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/m² 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/m² 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/m² 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 mcg/m² 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 mcg/m² 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/m² 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.

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/m² basis at a maternal dose of 100 mcg/kg and 300 mcg/kg to rats and rabbits, respectively).

Nursing Mothers

DYMISTA: It is not known whether DYMISTA is excreted in human breast 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 by nursing mothers, based on data from 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 tritiated fluticasone propionate (less than the maximum recommended daily intranasal dose in adults on a mcg/m² basis) resulted in measurable radioactivity in the milk.

Pediatric Use

Use of DYMISTA for seasonal allergic rhinitis in pediatric patients 6 to 11 years of age is supported by safety and efficacy data from clinical studies (416 patients 6 to 11 years of age with allergic rhinitis were treated with DYMISTA in controlled clinical trials) and the established efficacy and safety of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in this age group.

Sixty-one patients ages 4-5 years of age were treated with DYMISTA in the pediatric studies described above. Safety findings in children 4-5 years of age were similar to those in children 6-11 years of age, but efficacy was not established.

Safety and effectiveness of DYMISTA has not been studied in pediatric patients below the age of 4 years.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids,

including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including DYMISTA, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives.

Geriatric Use

Clinical trials of DYMISTA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Patient Information and Instructions for Use*)

Somnolence

Somnolence has been reported in some patients (8 of 1,269 patients) taking DYMISTA in controlled clinical trials. Caution patients against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as driving or operating machinery after administration of DYMISTA.

Concurrent Use of Alcohol and other Central Nervous System Depressants

Advise patients to avoid concurrent use of DYMISTA with alcohol or other central nervous system depressants because additional reductions in alertness and additional impairment of central nervous system performance may occur.

Local Nasal Effects

Nasal corticosteroids are associated with epistaxis, nasal ulceration, nasal septal perforation, *Candida albicans* infection and impaired wound healing. Patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use DYMISTA until healing has occurred.

Glaucoma and Cataracts

Inform patients that glaucoma and cataracts are associated with nasal and inhaled corticosteroid use. Advise patients to inform his/her health care provider if a change in vision is noted while using DYMISTA.

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Inform patients of potential worsening of existing tuberculosis, fungal, bacterial, viral or parasitic infections, or ocular herpes simplex.

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.

Priming

Instruct patients to shake the bottle gently before each use and prime the pump before initial use and when DYMISTA has not been used for 14 or more days.

Keep Spray Out of Eyes

Instruct patients to avoid spraying DYMISTA into their eyes.

Keep Out of Children's Reach

Instruct patients to keep DYMISTA out of the reach of children. If a child accidentally ingests DYMISTA, seek medical help or call a poison control center immediately.

Potential Drug Interactions

Advise patients that coadministration of DYMISTA and ritonavir is not recommended and to be cautious if DYMISTA is coadministered with ketoconazole.

Rx only

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