DYMISTA- azelastine hydrochloride and fluticasone propionate spray, metered
Viatris Specialty LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DYMISTA® safely and effectively. See full prescribing information for DYMISTA.

DYMISTA (azelastine hydrochloride and fluticasone propionate) nasal spray
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

Contraindications (4) 12/2024

INDICATIONS AND USAGE

DYMISTA contains an H_1-receptor antagonist and a corticosteroid, and is indicated for the relief of symptoms of seasonal allergic rhinitis in adult and pediatric patients 6 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 1 spray per nostril twice daily (2.1)
- For nasal use only. (2.2)
- Prime before initial use and when it has not been used for 14 or more days. (2.2)

DOSAGE FORMS AND STRENGTHS

Nasal spray: 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate in each spray. (3)

CONTRAINDICATIONS

Hypersensitivity to azelastine hydrochloride, fluticasone propionate, or to any ingredients of DYMISTA. Reactions have included anaphylaxis. (4)

WARNINGS AND PRECAUTIONS

- Somnolence: Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking DYMISTA. (5.1)
- 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. (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)
- 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 slowly. (5.5)
- Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving DYMISTA. (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.
- Ritonavir: Coadministration is not recommended. (5.6, 7.2)
- Other potent CYP3A4 inhibitors, such as ketoconazole: use caution with coadministration. (5.6, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 12/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DYMISTA is indicated for the relief of symptoms of seasonal allergic rhinitis in adult and pediatric patients 6 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of DYMISTA is 1 spray (137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate) in each nostril twice daily.

2.2 Important Administration Instructions

- Administer DYMISTA by the nasal route only.
- Shake the bottle gently before each use.
- Avoid spraying DYMISTA into the eyes. If sprayed in the eyes, flush eyes with water for at least 10 minutes.

Priming

Prime DYMISTA before initial use by releasing 6 sprays or until a fine mist appears.

Repriming (as needed)

When DYMISTA has not been used for 14 or more days, reprime with 1 spray or until a fine mist appears.

3 DOSAGE FORMS AND STRENGTHS

Nasal spray: 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate per spray.

4 CONTRAINDICATIONS

DYMISTA is contraindicated in patients with hypersensitivity to azelastine hydrochloride, fluticasone propionate, or to any other ingredients of DYMISTA. Reactions have included anaphylaxis *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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 placebo controlled trials *[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. 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 *[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 than those who received placebo *[see Adverse Reactions (6)]*.

Instances of nasal ulceration and nasal septal perforation have been reported in patients following the nasal 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 nasally, 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.

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 (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).

5.4 Immunosuppression and Risk of Infections

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 Prescribing Information for VZIG and IG.) 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 Hypercorticism and Adrenal Suppression

When nasal 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 nasal 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 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 *[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 *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- 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)]*
- Glaucoma and Cataracts *[see Warnings and Precautions (5.3)]*
- Immunosuppression and Risk of Infections *[see Warnings and Precautions (5.4)]*
- Hypercorticism and Adrenal Suppression, 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.

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) *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.1)]*.

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 reactions.

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 (≥ 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 reactions. There were two reports of somnolence, one severe, among children taking DYMISTA *[see Warnings and Precautions (5.1)]*.

6.2 Postmarketing Experience

The following spontaneous adverse reactions 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

Musculoskeletal and Connective Tissue Disorders: growth suppression *[see Use in Specific Populations (8.4)]*

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

7 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.

7.1 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 *[see Warnings and Precautions (5.1)]*.

7.2 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 *[see 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 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data from postmarketing experience with DYMISTA in pregnant women have not identified any drug associated risks of miscarriage, birth defects, or other adverse maternal or fetal outcomes. The individual components of DYMISTA have been marketed for decades. While the data regarding the use of nasal preparations of fluticasone

propionate in pregnancy are limited, data from clinical studies of inhaled fluticasone propionate do not indicate an increased risk of adverse maternal or fetal outcomes.

Animal reproduction studies with DYMISTA are not available; however, studies are available with its individual components, azelastine hydrochloride and fluticasone propionate. In animal reproduction studies, there was no evidence of fetal harm in animals at oral doses of azelastine hydrochloride approximately 10 times the clinical daily dose. Oral administration of azelastine hydrochloride to pregnant mice, rats, and rabbits, during the period of organogenesis, produced developmental toxicity that included structural abnormalities, decreased embryo-fetal survival, and decreased fetal body weights at doses 530 times and higher than the maximum recommended human daily nasal dose (MRHDID) of 0.548 mg. However, the relevance of these findings in animals to pregnant women was considered questionable based upon the high animal to human dose multiple.

In animal reproduction studies, fluticasone propionate administered via nose-only inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m^2 basis. Teratogenicity, characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the MRHDID of 200 mcg on a mcg/m^2 basis *(see Data).* Experience with corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Azelastine Hydrochloride: In an embryo-fetal development study in mice dosed during the period of organogenesis, azelastine hydrochloride caused embryo-fetal death, structural abnormalities (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification, and decreased fetal weight at approximately 610 times the MRHDID in adults (on a mg/m^2 basis at a maternal oral dose of 68.6 mg/kg/day), which also caused maternal toxicity as evidenced by decreased maternal body weight. Neither fetal nor maternal effects occurred in mice at approximately 25 times the MRHDID in adults (on a mg/m^2 basis at a maternal oral dose of 3 mg/kg/day).

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 7 to 17, azelastine hydrochloride caused structural abnormalities (oligo- and brachydactylia), delayed ossification, and skeletal variations, in the absence of maternal toxicity, at approximately 530 times the MRHDID in adults (on a mg/m^2 basis at a maternal oral dose of 30 mg/kg/day). Azelastine hydrochloride caused embryo-fetal death and decreased fetal weight and severe maternal toxicity at approximately 1200 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 68.6 mg/kg/day). Neither fetal nor maternal effects occurred at approximately 55 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 3 mg/kg/day).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6 to 18, azelastine hydrochloride caused abortion, delayed ossification and decreased fetal weight and severe maternal toxicity at approximately 1100 times the MRHDID in adults (on a mg/m^2 basis at a maternal oral dose of 30 mg/kg/day). Neither fetal nor maternal effects occurred at approximately 10 times the MRHDID (on a mg/m^2 basis at a maternal oral dose of 0.3 mg/kg/day).

In a prenatal and postnatal development study in pregnant rats dosed from late in the gestation period and through the lactation period from gestation day 17 through lactation day 21, azelastine hydrochloride produced no adverse developmental effects on pups at maternal doses up to approximately 530 times the MRHDID (on mg/m^2 basis at a maternal dose of 30 mg/kg/day).

Fluticasone Propionate: In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately 5 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). Neither fetal nor maternal effects occurred in rats at approximately 1 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 1 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). Neither fetal nor maternal effects occurred in mice with a dose approximately 0.4 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the nose-only inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 1 times the MRHDID (on a mg/m^2 basis with a maternal nose-only inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. Neither fetal nor maternal effects occurred in rats with a dose approximately 0.25 times the MRHDID (on a mg/m^2 basis with a maternal nose-only inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately 0.06 times the MRHDID and higher (on a mg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at dose approximately 0.4 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). Neither fetal nor maternal effects occurred in rabbits with a dose approximately 0.01 times the MRHDID (on a mg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 2 times the MRHDID (on a mg/m^2 basis with maternal subcutaneous doses up to 50

mcg/kg/day).

8.2 Lactation

Risk Summary

There are no available data on the presence of azelastine hydrochloride or fluticasone propionate in human milk, the effects on the breastfed infant, or the effects on milk production. Breastfed infants should be monitored for signs of milk rejection during DYMISTA use by lactating women *(see Clinical Considerations)*. Fluticasone propionate is present in rat milk *(see Data).* Other corticosteroids have been detected in human milk. However, fluticasone propionate concentrations in plasma after nasal therapeutic doses are low and therefore concentrations in human breast milk are likely to be correspondingly low *[see Clinical Pharmacology (12.3)].* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DYMISTA and any potential adverse effects on the breastfed infant from DYMISTA or from the underlying maternal condition.

Clinical Considerations

Monitoring for Adverse Reactions

Breastfed infants of lactating women treated with DYMISTA should be monitored for possible signs of milk rejection related to the bitter taste of azelastine hydrochloride.

Data

Subcutaneous administration of 10 mcg/kg of tritiated fluticasone propionate to lactating rats resulted in measurable radioactivity in the milk.

8.4 Pediatric Use

The safety and effectiveness of DYMISTA for seasonal allergic rhinitis have been established in pediatric patients aged 6 years and older. Use of DYMISTA for this indication in pediatric patients 6 to 11 years of age is supported by evidence from controlled clinical trials (416 patients 6 to 11 years of age with allergic rhinitis were treated with DYMISTA) *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

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 effectiveness has not been established.

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

Controlled clinical studies have shown that nasal 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 nasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with nasal corticosteroids has not been adequately studied. The growth of

pediatric patients receiving nasal 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.

8.5 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.

10 OVERDOSAGE

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

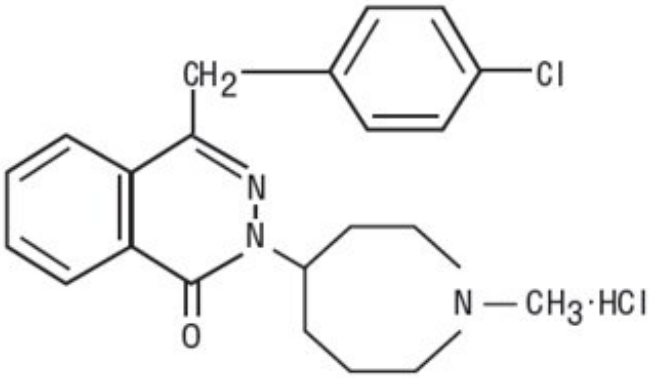
Azelastine Hydrochloride: There have been no reported overdosages with azelastine hydrochloride. Acute azelastine hydrochloride overdosage by adults with this dosage form is unlikely to result in clinically significant adverse reactions, other than increased somnolence, since one (1) 23 g bottle of DYMISTA contains approximately 23 mg of azelastine hydrochloride. 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.

Fluticasone Propionate: Chronic fluticasone propionate overdosage may result in signs/symptoms of hypercorticism *[see Warnings and Precautions (5.5)]*.

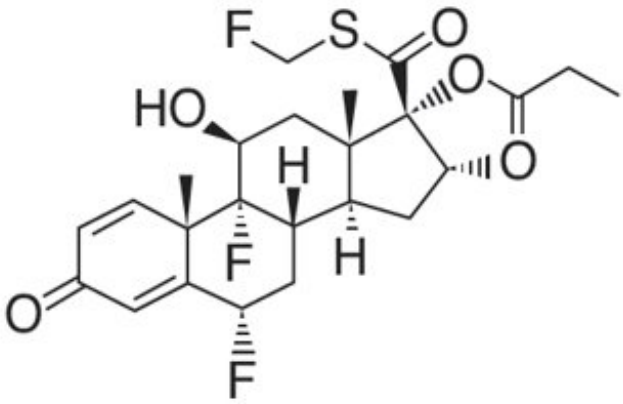
11 DESCRIPTION

DYMISTA (azelastine hydrochloride and fluticasone propionate) nasal spray is formulated as a white, uniform metered-spray suspension for nasal administration. It is a fixed dose combination product containing an antihistamine (H_1 receptor antagonist) and a corticosteroid as active ingredients.

Azelastine hydrochloride active ingredient occurs as a white, odorless, crystalline powder with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerin. It has a melting point of 225°C and the pH of 5.2. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is $C_{22}H_{24}ClN_3O \cdot HCl$ with the following chemical structure:



Fluticasone propionate active ingredient is a white powder with a melting point of 273°C, a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol. Fluticasone propionate is a synthetic corticosteroid having the chemical name S-(fluoromethyl)-6α,9α-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate, and the following chemical structure:



DYMISTA (azelastine hydrochloride and fluticasone propionate) nasal spray, 137 mcg/50 mcg contains 0.1% solution of azelastine hydrochloride and 0.037% suspension of micronized fluticasone propionate in an isotonic aqueous suspension containing benzalkonium chloride (0.1 mg/g), carboxymethylcellulose sodium, edetate disodium, glycerin, microcrystalline cellulose, phenylethyl alcohol (2.5 mg/g), polysorbate 80, and purified water. It has a pH of approximately 6.0.

After priming *[see Dosage and Administration (2.2)]*, each metered spray delivers a 0.137 mL mean volume of suspension containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg of azelastine base) and 50 mcg of fluticasone propionate. The 23 g bottle provides 120 metered sprays, after priming.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 (histamine H_1-receptor antagonist and 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 than dexamethasone in these assays. Data from the McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity. The clinical relevance of these findings is unknown.

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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a placebo-controlled trial (95 patients with allergic rhinitis), there was no evidence of an effect of azelastine hydrochloride nasal spray (2 sprays per nostril twice daily for 56 days) on cardiac repolarization as represented by the corrected QT interval (QTc) of the electrocardiogram. Following multiple dose oral administration of azelastine 4 mg or 8 mg twice daily, the mean change in QTc was 7.2 msec and 3.6 msec, respectively.

Interaction studies investigating the cardiac repolarization effects of concomitantly administered oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. These drugs had no effect on QTc based on analysis of serial electrocardiograms.

12.3 Pharmacokinetics

Absorption

After nasal administration of two sprays per nostril (548 mcg of azelastine hydrochloride and 200 mcg of fluticasone) of DYMISTA, the mean (± standard deviation) peak plasma exposure (C_{max}) was 194.5 ± 74.4 pg/mL for azelastine and 10.3 ± 3.9 pg/mL for

fluticasone propionate and the mean total exposure (AUC) was 4217 ± 2618 pg/mL*hr for azelastine and 97.7 ± 43.1 pg/mL*hr for fluticasone. The median time to peak exposure (t_{max}) from a single dose was 0.5 hours for azelastine and 1.0 hours for fluticasone.

Systemic bioavailability of azelastine from DYMISTA following nasal administration was comparable with monotherapy azelastine hydrochloride (Astelin®) nasal spray (i.e., approximately 40%). Systemic bioavailability of fluticasone from DYMISTA following nasal administration was 44-61% higher than monotherapy fluticasone propionate (bioavailability for monotherapy fluticasone nasal spray was less than 2%). Due to the low nasal bioavailability, pharmacokinetic data for fluticasone propionate were obtained via other routes of administration. Studies using oral dosing of radiolabeled fluticasone propionate showed negligible oral bioavailability and high extraction from plasma. The majority of the circulating radioactivity was due to an inactive metabolite.

Distribution

Based on intravenous and oral administration, the steady-state volume of distribution of azelastine hydrochloride is 14.5 L/kg. *In vitro* studies with human plasma indicate that the plasma protein binding of azelastine hydrochloride and its metabolite, desmethylazelastine, are approximately 88% and 97%, respectively.

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% with no obvious concentration relationship. Fluticasone propionate is weakly and reversibly bound to erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propionate is not significantly bound to human transcortin.

Elimination

Following nasal administration of DYMISTA, the elimination half-life of azelastine hydrochloride is approximately 25 hours. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine.

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Metabolism

Azelastine hydrochloride is oxidatively metabolized to the principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The specific P450 isoforms responsible for the biotransformation of azelastine have not been identified. The total clearance of azelastine is approximately 0.50 L/kg/hr.

For fluticasone propionate, the only circulating metabolite detected in man is the 17β-carboxylic acid derivative, which is formed through the CYP3A4 pathway. This inactive metabolite had less affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological

activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man. The average total clearance of fluticasone propionate is relatively high (approximately 66 L/hr).

Specific Populations

DYMISTA was not studied in any specific populations, and no gender-specific pharmacokinetic data have been obtained.

Following oral administration of azelastine hydrochloride, pharmacokinetic parameters were not influenced by hepatic impairment, age, or gender. The effect of race has not been evaluated.

Patients with Renal Impairment

Based on oral, single-dose studies of azelastine hydrochloride, renal impairment (creatinine clearance < 50 mL/min) resulted in a 70-75% higher C_{max} and AUC compared to healthy subjects. Time to maximum concentration was unchanged.

Drug Interaction Studies

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.

Erythromycin

Coadministration of orally administered azelastine (4 mg twice daily) with erythromycin (500 mg three times daily for 7 days) resulted in C_{max} of 5.36 ± 2.6 ng/mL and AUC of 49.7 ± 24 ng•h/mL for azelastine, whereas, administration of azelastine alone resulted in C_{max} of 5.57 ± 2.7 ng/mL and AUC of 48.4 ± 24 ng•h/mL for azelastine.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg three times daily) did not affect fluticasone propionate pharmacokinetics.

Cimetidine and Ranitidine

In a multiple-dose, steady-state drug interaction trial in healthy subjects, cimetidine (400 mg twice daily) increased orally administered mean azelastine hydrochloride (4 mg twice daily) concentrations by approximately 65%. Coadministration of orally administered azelastine hydrochloride (4 mg twice daily) with ranitidine hydrochloride (150 mg twice daily) resulted in C_{max} of 8.89 ± 3.28 ng/mL and AUC of 88.22 ± 40.43 ng•h/mL for azelastine hydrochloride, whereas, administration of azelastine hydrochloride alone resulted in C_{max} of 7.83 ± 4.06 ng/mL and AUC of 80.09 ± 43.55 ng•h/mL for azelastine hydrochloride.

Theophylline

No significant pharmacokinetic interaction was observed with the coadministration of an oral 4 mg dose of azelastine hydrochloride twice daily and theophylline 300 mg or 400 mg twice daily.

Ritonavir

Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor, ritonavir, is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (< 10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/mL (range, 10.8 to 14.1 pg/mL) and AUC(0-τ) averaged 8.43 pg•hr/mL (range, 4.2 to 18.8 pg•hr/mL). Fluticasone propionate C_{max} and AUC(0-τ) increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other strong CYP3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol *[see Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

DYMISTA

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

Azelastine Hydrochloride

Two-year carcinogenicity studies in Crl:CD(SD)BR rats and NMRI mice were conducted to assess the carcinogenic potential of azelastine hydrochloride. No evidence of tumorigenicity was observed in rats at doses up to 30 mg/kg/day (approximately 530 and 240 times the MRHDID for adults and children, respectively, on a mg/m^2 basis). No evidence for tumorigenicity was observed in mice at doses up to 25 mg/kg (approximately 220 and 100 times the MRHDID for adults and children, respectively, 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.

There were no effects on male or female fertility and reproductive performance in male and female rats 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 25 and 10 times the MRHDID in adults and children, respectively, on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 3 and 1 times the MRHDID in adults and children, respectively, on a mcg/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.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 2 times the MRHDID for adults on a mcg/m^2 basis).

14 CLINICAL STUDIES

Adults and Adolescents 12 Years of Age and Older: The efficacy and safety of DYMISTA in adults and adolescents 12 years of age and older with seasonal allergic rhinitis was evaluated in 3 randomized, multicenter, double-blind, placebo-controlled clinical trials in 853 patients. The population of the trials was 12 to 78 years of age (64% female, 36% male; 80% white, 16% black, 2% Asian, 1% other).

Patients were randomized to one of four treatment groups: one spray per nostril twice daily of DYMISTA, azelastine hydrochloride nasal spray, fluticasone propionate nasal spray, and vehicle placebo. The azelastine hydrochloride and fluticasone propionate comparators use the same device and vehicle as DYMISTA and are not commercially marketed. Assessment of efficacy was based on the reflective total nasal symptom score (rTNSS), in addition to the instantaneous total nasal symptom score (iTNSS) and other supportive secondary efficacy variables. TNSS is calculated as the sum of the patients' scoring of the 4 individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Patients were required to record symptom severity daily reflecting over the previous 12 hours (morning, AM, and evening, PM). For the primary efficacy endpoint, the combined AM+PM rTNSS (maximum score of 24) was assessed as a change from baseline for each day and then averaged over a 2-week treatment period. The primary efficacy endpoint was the mean change from baseline in combined AM+PM rTNSS over 2 weeks. The iTNSS was recorded immediately prior to the next dose.

In these trials, DYMISTA demonstrated statistically significant greater decreases in rTNSS as compared to azelastine hydrochloride and to fluticasone propionate, as well as to placebo. The differences between the monotherapies and placebo also were statistically significant. Representative results from one of the trials are shown below (Table 3).

Table 3. Mean Change from Baseline in Reflective Total Nasal Symptom Scores Over 2 Weeks* in Adults and Children ≥ 12 Years with Seasonal Allergic Rhinitis

		Baseline	Change from	Difference from DYMISTA Nasal Spray

			Baseline			
Treatment (one spray/nostril twice daily)	N	LS Mean	LS Mean	LS Mean	95% CI	*P-value*
DYMISTA	207	18.3	-5.6	--	--	--
Azelastine HCl Nasal Spray†	208	18.3	-4.3	-1.4	(-2.2, -0.5)	0.002
Fluticasone Propionate Nasal Spray†	207	18.2	-4.7	-1.0	(-1.8, -0.2)	0.022
Placebo	209	18.6	-2.9	-2.7	(-3.5, -1.9)	< 0.001

LS Mean, 95% CI, and p-value are obtained from the repeated-measures analysis of covariance model using observed data.

* Sum of AM and PM rTNSS for each day (Maximum Score = 24) and averaged over the 14 day treatment period

† Not commercially marketed

In these trials, DYMISTA also demonstrated statistically significant, greater decreases in iTNSS as compared to placebo, as did the azelastine hydrochloride and fluticasone propionate comparators. Representative results from one of the trials are shown below (Table 4).

Table 4. Mean Change from Baseline in Instantaneous Total Nasal Symptom Scores Over 2 Weeks* in Adults and Children ≥ 12 Years with Seasonal Allergic Rhinitis

		Baseline	Change from Baseline	Difference from Placebo		
Treatment (one spray/nostril twice daily)	N	LS Mean	LS Mean	LS Mean	95% CI	*P-value*
DYMISTA	207	17.2	-5.6	--	--	--
Azelastine HCl Nasal Spray†	208	16.8	-4.3	-1.4	(-2.2, -0.5)	0.002
Fluticasone Propionate Nasal Spray†	207	16.8	-4.7	-1.0	(-1.8, -0.2)	0.022
Placebo	209	17.3	-2.9	-2.7	(-3.5, -1.9)	< 0.001

LS Mean, 95% CI, and p-value are obtained from the repeated-measures analysis of covariance model using observed data.

* Sum of AM and PM rTNSS for each day (Maximum Score = 24) and averaged over the 14 day treatment period

† Not commercially marketed

Onset of action, defined as the first timepoint at which DYMISTA was statistically superior to placebo in the mean change from baseline in iTNSS and which was sustained thereafter, was assessed in each of the three trials. Onset of action was observed as early as 30 minutes following the initial dose of DYMISTA.

The subjective impact of seasonal allergic rhinitis on patient's health-related quality of life was evaluated by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (28 items in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional) evaluated on a 7-point scale where 0 = no impairment and 6 = maximum impairment), which was administered to patients 18 years

of age and older. An overall RQLQ score is calculated from the mean of all items in the instrument. A change from baseline of at least 0.5 points is considered a clinically meaningful improvement. In each of these trials, DYMISTA demonstrated a statistically significant greater decrease from baseline in the overall RQLQ than placebo, which ranged from -0.55 (95% CI -0.72, -0.39) to -0.80 (95% CI -1.05, -0.55). In these trials, the treatment differences between DYMISTA and the monotherapies were less than the minimum important difference of 0.5 points.

Pediatric Patients 6-11 Years of Age: The efficacy and safety of DYMISTA was evaluated in one randomized, multi-center, double-blind, placebo-controlled trial in 304 children 6 to 11 years of age with seasonal allergic rhinitis. Patients were randomized 1:1 to receive either one spray per nostril twice daily of DYMISTA or placebo (vehicle control) for 14 days. The design of this trial was similar to that of the adult trials.

The primary efficacy endpoint was the mean change from baseline in combined AM+PM reflective total nasal symptom score (rTNSS) over 2 weeks. DYMISTA was not statistically significantly different than placebo, but the results were numerically supportive (Table 5).

Table 5: Mean Change from Baseline in Reflective Total Nasal Symptom Scores Over 2 Weeks in Children Age 6 to 11 Years

Treatment	Baseline	LS Mean Change from baseline	LS Mean Difference (95% CI)	P-value
DYMISTA N = 152	18.4	-3.7	-0.8 (-1.8, 0.2)	0.099
Placebo N = 152	18.0	-2.9		

CI = confidence interval
LS Mean, 95% CI, and p-value are obtained from the repeated-measures analysis of covariance model using observed data

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied: DYMISTA nasal spray (NDC 0037-0245-23) is supplied as an amber glass bottle fitted with a metered-dose spray pump unit. The spray pump unit consists of a nasal spray pump with a white nasal adapter and clear plastic dust cap. Each bottle contains a net fill weight of 23 g and will deliver 120 metered sprays after priming *[see Dosage and Administration (2.2)]*. After priming *[see Dosage and Administration (2.2)]*, each spray delivers a suspension volume of 0.137 mL as a fine mist, containing 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate (137 mcg/50 mcg). The correct amount of medication in each spray cannot be assured before the initial priming and after 120 sprays have been used, even though the bottle is not completely empty. The bottle should be discarded after 120 sprays have been used.

DYMISTA should not be used after the expiration date “EXP” printed on the bottle label and carton.

Storage: Store upright with the dust cap in place at controlled room temperature 20°C

to 25°C (68°F to 77°F). [See USP Controlled Temperature] Protect from light. Do not store in the freezer or refrigerator.

17 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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.2)]*.

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 *[see Warnings and Precautions (5.3)]*.

Immunosuppression and Risk of Infections: 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 *[see Warnings and Precautions (5.4)]*.

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 *[see Use in Specific Populations (8.4)]*.

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 *[see Dosage and Administration (2.2)]*.

Keep Spray Out of Eyes: Instruct patients to avoid spraying DYMISTA into their eyes.

Potential Drug Interactions: Advise patients that coadministration of DYMISTA and ritonavir is not recommended and to be cautious if DYMISTA is coadministered with ketoconazole *[see Drug Interactions (7.2)]*.

U.S. Patent 8,168,620

Manufactured by:
Cipla Ltd. Indore SEZ, Pithampur, India
M.L. No. 28/2/2010

Manufactured for:
MEDA
Meda Pharmaceuticals Inc.
Canonsburg, PA 15317 U.S.A.

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PATIENT INFORMATION

DYMISTA (*Dy-Mist-A*)
(azelastine hydrochloride and fluticasone propionate)
nasal spray

Important: For use in your nose only

What is DYMISTA?

- DYMISTA is a prescription medicine used to treat symptoms of seasonal allergic rhinitis in people 6 years of age and older.
- DYMISTA may help to reduce your nasal symptoms including stuffy nose, runny nose, itching, and sneezing.

It is not known if DYMISTA is safe or effective in children under 4 years of age.

Do not use DYMISTA if you:

- are allergic to azelastine hydrochloride, or fluticasone propionate, or any of the ingredients in DYMISTA. Stop using DYMISTA and get medical help right away if you have symptoms of a serious allergic reaction.
- See the end of the leaflet for a complete list of ingredients in DYMISTA.

Before using DYMISTA tell your healthcare provider about all of your medical conditions, including if you:

- have had recent nasal sores, nasal surgery, or nasal injury.
- have eye or vision problems, such as cataracts or glaucoma (increased pressure in your eye).
- have tuberculosis or any untreated fungal, bacterial, viral infections or eye infections caused by herpes.
- have been near someone who has chickenpox or measles.
- are not feeling well or have any other symptoms that you do not understand.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if DYMISTA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using DYMISTA.

Tell your healthcare provider about all the medicines you take, including

prescription and over-the-counter medicines, vitamins, and herbal supplements.

DYMISTA and other medicines may affect each other, causing side effects.

Especially tell your healthcare provider if you take:

- antifungal or anti-HIV medicines

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use DYMISTA?

- Read the **Instructions for Use** at the end of this leaflet for information about the right way to use DYMISTA.
- An adult should help a young child use DYMISTA**.**
- DYMISTA is for use in your nose only. Do not spray it into your eyes or mouth. If you spray DYMISTA into your eyes, flush your eyes with large amounts of water for 10 minutes and then call your healthcare provider.
- Use DYMISTA exactly as your healthcare provider tells you to use it. Your healthcare provider will tell you how much DYMISTA to use and when to use it.
- If a child accidentally swallows DYMISTA or you use too much DYMISTA, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while using DYMISTA?

- DYMISTA can cause sleepiness or drowsiness. Do not drive, operate machinery, or do anything that needs you to be alert until you know how DYMISTA affects you.
- Do not drink alcohol or take any other medicines that may cause you to feel sleepy while using DYMISTA. It can increase your chances of having serious side effects.

What are the possible side effects of DYMISTA?
DYMISTA may cause serious side effects including:

- **sleepiness or drowsiness.**
- **nasal problems.** Symptoms of nasal problems may include:
    - crusting in the nose
    - nosebleeds
    - runny nose
    - hole in the cartilage between your nose (nasal septal perforation). A whistling sound when you breathe may be a symptom of nasal septal perforation.
- **slow wound healing.** You should not use DYMISTA until your nose has healed if you have a sore in your nose, if you have had surgery on your nose, or if your nose has been injured.
- **thrush (candida), a fungal infection in your nose and throat.** Tell your healthcare provider if you have any redness or white colored patches in your nose or mouth.

- **eye problems, such as glaucoma or cataracts.** Some people may have eye problems, including glaucoma and cataracts. You should have regular eye exams when using DYMISTA.
- **immune system problems and increased risk of infections.** DYMISTA may cause problems with the way your immune system protects your body against infection and increase your risk of infection. Avoid contact with people who have contagious diseases such as chickenpox or measles while you use DYMISTA. Symptoms of infection may include:

    - fever
    - aches or pains
    - chills
    - feeling tired

- **adrenal insufficiency.** Adrenal insufficiency is a condition in which the adrenal glands do not make enough steroid hormones. Symptoms of adrenal insufficiency may include:

    - tiredness
    - weakness
    - nausea
    - vomiting
    - low blood pressure

- **slowed or delayed growth in children.** A child's growth should be checked regularly while using DYMISTA.

Call your healthcare provider or get medical help right away if you have symptoms of any of the serious side effects listed above.

The most common side effects of DYMISTA Nasal Spray include:

- changes in taste
- nosebleeds
- headache

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of DYMISTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DYMISTA?

- Store DYMISTA upright with the dust cap in place at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze or refrigerate DYMISTA.
- Protect DYMISTA from light.
- Do not use DYMISTA after the expiration date “EXP” printed on the bottle label and carton.
- Throw away your DYMISTA bottle after using 120 sprays after initial priming. Even though the bottle may not be completely empty, you may not get the correct dose

of medicine if you continue to use it.

Keep DYMISTA and all medicines out of reach of children.

General information about the safe and effective use of DYMISTA
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use DYMISTA for a condition for which it was not prescribed. Do not give DYMISTA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about DYMISTA that is written for health professionals.

What are the ingredients in DYMISTA?
Active ingredients: azelastine hydrochloride and fluticasone propionate
Inactive ingredients: benzalkonium chloride, carboxymethylcellulose sodium, edetate disodium, glycerin, microcrystalline cellulose, phenylethyl alcohol, polysorbate 80, and purified water.

For more information, go to www.DYMISTA.com or call Meda Pharmaceuticals Inc. at 1-888-939-6478.

Instructions for Use

DYMISTA (*Dy-Mist-A*)
(azelastine hydrochloride and fluticasone propionate)
nasal spray

For use in your nose only. Do not spray in your eyes.

Read the Instructions for Use before you start to use DYMISTA and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment. Before you use DYMISTA, make sure your healthcare provider shows you the right way to use it.

Shake the bottle gently before each use.

Your DYMISTA pump. (See Figure A)

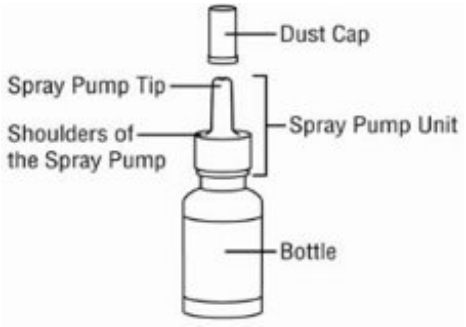

Figure A

Instructions for Using Your DYMISTA Pump.

Before you use DYMISTA for the first time, you will need to shake the bottle gently and prime the pump.

For use in young children: An adult should help a young child use DYMISTA. (See Steps 1 through 12).

Priming your DYMISTA pump
Before you prime the bottle, shake it gently.

Step 1.

Remove the clear plastic dust cap from the spray pump tip of the bottle. **(See Figure B)**

Figure B

Step 2.

Hold the bottle upright with two fingers on the shoulders of the spray pump unit and put your thumb on the bottom of the bottle. Press upward with your thumb and release for the pumping action.

- Repeat the pumping action until you see a fine mist. You should see a fine mist of the medicine after 6 pumps or less. **(See Figure C)**
- To get a fine mist of medicine, you must repeat the pumping action fast and use firm pressure against the bottom of the bottle.
- If you see a stream of liquid, the spray will not work right and may cause nasal discomfort.
- If you do not use DYMISTA for 14 or more days, you will need to shake the bottle gently, and prime the pump with 1 spray or until you see a fine mist. If you do not see a fine mist, clean the tip of the spray nozzle. See the cleaning section below.
- **Once you see the fine mist of medicine, your DYMISTA pump is ready for use.**

Figure C

Using your DYMISTA:

For use in young children: An adult should help a young child use DYMISTA.

Step 3.

Gently blow your nose to clear nostrils. **(See Figure D)**

Figure D

Step 4.

Shake the bottle gently. Close 1 nostril with a finger. Tilt your head forward slightly. Keep the bottle upright and carefully place the spray pump tip ¼ to ½ inch into your other nostril. **(See Figure E)**

Figure E

Step 5.

For each spray firmly press the pump 1 time. Keep your head tilted down and at the same time, gently breathe in through your nostril. **(See Figure F)**

Do not spray directly onto the nasal septum (the wall between your 2 nostrils).

- Repeat Step 5 in your other nostril.
- **Do not tilt your head back.** This will help to keep the medicine from going into your throat.
- If the medicine goes into your throat you may get a bitter taste in your mouth. This is normal.

Figure F

Step 6.

When you finish using DYMISTA, wipe the spray tip with a clean tissue or cloth. Put the dust cap back on the spray pump tip of the bottle. **(See Figure G)**

Figure G

Each bottle of DYMISTA contains enough medicine for you to spray medicine from the bottle 120 times. **After initial priming, do not use your bottle of DYMISTA after 120 sprays.** You may not receive the right amount of medicine. Keep track of the number of sprays you use from your bottle of DYMISTA and throw away the bottle even if it has medicine left in it.

Do not count any sprays used for initially priming the bottle.

Cleaning the Spray Pump Tip:

Your DYMISTA should be cleaned at least 1 time each week. To do this:

Step 7.

Remove the dust cap and then gently pull upward on the spray pump unit to remove it from the bottle. **(See Figure H)**

Figure H

Step 8.

Wash the spray pump unit and dust cap in warm tap water. **(See Figure I)**

Figure I

Step 9.

Allow to dry completely. When dry, place the spray pump unit and dust cap back on the bottle. **(See Figure J)**

Figure J

Step 10.

If the spray pump unit becomes blocked, it can be removed as instructed above in Step 7 and placed in warm water to soak.

Do not try to unblock the spray pump unit by inserting a pin or other sharp object. This will damage the spray pump unit and cause you not to get the right dose of medicine.

Step 11.

After the spray pump unit is unblocked, rinse the applicator and cap with cold water, and allow them to dry as in Step 10 above. When dry, place the spray pump unit back on the bottle and put the dust cap on the spray pump tip.

Step 12.

Reprime the bottle as in Steps 1 and 2 above. Replace the dust cap and your DYMISTA is ready for use.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

U.S. Patent 8,168,620

Manufactured by:
Cipla Ltd. Indore SEZ, Pithampur, India
M.L. No. 28/2/2010

Manufactured for:
MEDA
Meda Pharmaceuticals Inc.
Canonsburg, PA 15317 U.S.A.

DYMISTA is a registered trademark of Meda Pharmaceuticals Inc., a Viatris Company.

Revised: 12/2024

IN-023A6-05N

PRINCIPAL DISPLAY PANEL - 137 mcg/50 mcg per Spray

NDC 0037-0245-23

Dymista®
(azelastine hydrochloride
and
fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

120 Metered Sprays

FOR NASAL USE ONLY

Rx Only

23 g net fill weight

Shake the bottle gently
before each use.

Each spray delivers 0.137 mL
(137 mcg azelastine
hydrochloride and 50 mcg
fluticasone propionate).

Contents: An aqueous
suspension containing azelastine
hydrochloride, fluticasone
propionate, glycerin,
microcrystalline cellulose and
carboxymethylcellulose sodium,
phenylethyl alcohol (2.5 mg/g),
edetate disodium, benzalkonium
chloride (0.1 mg/g), polysorbate
80 and purified water, pH 6.

Dosage: See enclosed full Prescribing Information.

Storage:
Store upright, with dust cap in place, at controlled room temperature 20°C to 25°C (68°F to 77°F). Protect from light. Do not store in the freezer or refrigerator.

Keep away from children.

FOR NASAL USE ONLY

Read PATIENT INSTRUCTIONS FOR USE for additional information on how to use the product.

Dosing Instructions

CLEAR YOUR NOSE

Clear your nostrils by gently blowing your nose.

LOOK AT YOUR TOES

Tilt your head down to keep the medicine from going into your throat.

SPRAY AND SNIFF GENTLY

Shake the bottle gently before each use.

Spray a fine mist, once per nostril.

Remember to sniff gently.

Discard after 120 actuations.

For assistance call **1-888-939-6478**
www.DYMISTA.com

DYMISTA is a registered trademark of Meda Pharmaceuticals Inc., a Viatris Company.

Shake the bottle gently before each use.

Initial Priming: 6 sprays or until a fine mist appears.

Repriming (only if you have not used Dymista for 14 or more days): 1 spray or until a fine mist appears.

FOR NASAL USE ONLY

Manufactured by: Cipla Ltd.,
Indore SEZ, Pithampur, India

M.L. No. 28/2/2010

For: Meda Pharmaceuticals Inc.
Canonsburg, PA 15317 U.S.A.

UC-023A6-04N

U.S. Patent 8,168,620

Read PATIENT INSTRUCTIONS FOR USE for additional information on how to use the product.

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For assistance call 1-888-939-6478
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Dymista®

(azelastine hydrochloride and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

Shake the bottle gently before each use.

Initial Priming: 6 sprays or until a fine mist appears.

Repriming (only if you have not used Dymista for 14 or more days): 1 spray or until a fine mist appears.

FOR NASAL USE ONLY

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Canonsburg, PA 15317 U.S.A.

UC-023A6-04N
U.S. Patent 8,168,620

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Dymista®

(azelastine hydrochloride and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

Each spray delivers 0.137 mL (137 mcg azelastine hydrochloride and 50 mcg fluticasone propionate).

Contents: An aqueous suspension containing azelastine hydrochloride, fluticasone propionate, glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, phenylethyl alcohol (2.5 mg/g), edetate disodium, benzalkonium chloride (0.1 mg/g), polysorbate 80 and purified water, pH 6.

Dosage: See enclosed full Prescribing Information.

Storage:
Store upright, with dust cap in place, at controlled room temperature 20°C to 25°C (68°F to 77°F). Protect from light. Do not store in the freezer or refrigerator.

Keep away from children.

FOR NASAL USE ONLY

NDC 0037-0245-23

Dymista®

(azelastine hydrochloride and fluticasone propionate)
Nasal Spray
137 mcg / 50 mcg per spray

120 Metered Sprays
FOR NASAL USE ONLY
Rx Only
23 g net fill weight

Shake the bottle gently before each use.

DYMISTA

azelastine hydrochloride and fluticasone propionate spray, metered

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0037-0245
Route of Administration	NASAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AZELASTINE HYDROCHLORIDE (UNII: 0L591QR10I) (AZELASTINE - UNII:ZQI909440X)	AZELASTINE HYDROCHLORIDE	137 ug
FLUTICASONE PROPIONATE (UNII: O2GMZ0LF5W) (FLUTICASONE - UNII:CUT2W21N7U)	FLUTICASONE PROPIONATE	50 ug

Inactive Ingredients

Ingredient Name	Strength
GLYCERIN (UNII: PDC6A3C0OX)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED (UNII: K679OBS311)	
PHENYLETHYL ALCOHOL (UNII: ML9LGA7468)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0037-0245-23	1 in 1 BOX	10/01/2016	
1		120 in 1 BOTTLE, SPRAY; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202236	10/01/2016	

Labeler - Viatris Specialty LLC (117455616)

Revised: 12/2024 Viatris Specialty LLC