PRODUCT MONOGRAPH

Pr**DYMISTA®**

Azelastine Hydrochloride and Fluticasone Propionate Suspension Nasal Spray

137 mcg/50 mcg per metered spray

Antihistamine and Corticosteroid Agent

BGP Pharma ULC
85 Advance Road
Etobicoke, ON
M8Z 2S6

Date of Revision: October 3, 2019

Submission Control No: 221498

Table of Contents

PrDYMISTA®

Azelastine Hydrochloride and Fluticasone Propionate Suspension Nasal Spray

137 mcg/50 mcg per metered spray

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
intranasal	Suspension for nasal spray / 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate per metered spray	benzalkonium chloride, carmellose sodium, disodium edetate, glycerol, microcrystalline cellulose, phenylethyl alcohol, polysorbate 80 and purified water

INDICATIONS AND CLINICAL USE

DYMISTA® (azelastine hydrochloride/fluticasone propionate) is indicated for

- the symptomatic treatment of moderate to severe seasonal allergic rhinitis (SAR) and associated ocular symptoms in adults, adolescents, and children aged 6 years and older for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient.

Pediatrics (< 6 years of age):
DYMISTA is not recommended for use in children less than 6 years of age as safety and efficacy have not been established in this age group.

CONTRAINDICATIONS

DYMISTA is contraindicated in patients who:

- are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see the DOSAGE FORMS, COMPOSITION AND PACKAGING for a complete listing).
- have untreated fungal, bacterial, or tuberculosis infections of the respiratory tract.

WARNINGS AND PRECAUTIONS

General

Systemic effects with nasal corticosteroids have been reported, particularly at high doses prescribed for prolonged periods. These effects are less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, reduction in bone density cataract, and glaucoma.

Although systemic effects have been minimal with recommended doses of fluticasone propionate, potential risk increases with larger doses. Therefore, larger than recommended doses of DYMISTA nasal spray should be avoided.

Central Nervous System Effects

Somnolence

In clinical trials, the occurrence of somnolence has been reported in some patients (7 of 1006 adult and adolescent patients and 2 of 416 children) taking DYMISTA Nasal Spray (see ADVERSE REACTIONS). Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as operating machinery or driving a motor vehicle after administration of DYMISTA Nasal Spray. Concurrent use of DYMISTA Nasal Spray with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur (see DRUG INTERACTIONS: Drug-Lifestyle Interactions).

Ear/Nose/Throat

Local Nasal Effects

In clinical trials of 2 weeks' duration, epistaxis was observed more frequently in patients treated with DYMISTA Nasal Spray than those who received placebo (see ADVERSE REACTIONS).

Instances of nasal ulceration and nasal septal perforation may occur in patients following the intranasal application of corticosteroids.

Wound Healing

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

Candida Infections

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

Endocrine and Metabolism

HPA Axis Effects
Use of excessive doses of corticosteroids may lead to signs or symptoms of hypercorticism and/or suppression of HPA function. 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.

Effects on Growth
Reduced growth velocity has been observed in children treated with intranasal corticosteroids. Therefore, children and adolescents should be maintained on the lowest dose at which effective control of symptoms is maintained.

Physicians should closely follow the growth of children and adolescents taking corticosteroids, by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed.

Steroid Replacement
The replacement of a systemic steroid with fluticasone propionate must be gradual and carefully supervised by the physician. The guidelines under "DOSAGE AND ADMINISTRATION" should be followed in all such cases.

If there is any reason to believe that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to DYMISTA.

Hepatic/Biliary/Pancreatic
Fluticasone propionate undergoes extensive first-pass metabolism by the liver enzyme cytochrome P450 3A4 (CYP3A4), therefore the systemic exposure of DYMISTA in patients with liver disease may be increased. This may result in a higher frequency of systemic adverse events. Caution is advised when treating these patients. (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Ritonavir (a highly potent CYP 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY). During postmarketing use of fluticasone propionate, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects. Co-treatment with other CYP 3A4 inhibitors, including cobicistat-containing products, is also expected to increase the risk of systemic side-effects. Therefore, concomitant use of DYMISTA and strong CYP 3A4 inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Immune
Patients who are on drugs that suppress the immune system, such as corticosteroids, are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune patients on corticosteroids. In such

patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects 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), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localized infections has been observed during corticosteroid therapy; this may require treatment with appropriate therapy or stopping the administration of DYMISTA nasal spray. DYMISTA nasal spray should not be used in patients with tuberculosis of the respiratory tract (see CONTRAINDICATIONS), and should be used with caution, if at all, in patients with 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.

Ophthalmologic

Dryness and irritation of the eyes, conjunctivitis, blurred vision, and rare instances of glaucoma, cataracts and increased intra-ocular pressure have been reported following administration of intranasal corticosteroids, as a class effect.

Visual disturbance may be reported with systemic and topical (including intranasal, inhaled and intraocular) corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Close monitoring is warranted in patients with a change in vision or with a history of increased ocular pressure, glaucoma, and/or cataracts.

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

Psychological and behavioural

Although rare, there is a potential of psychological and behavioural effects (particularly in children) including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression which have been reported for intranasal corticosteroids.

Special Populations

Pregnant Women: There are no or limited amount of data from the use of azelastine hydrochloride and fluticasone propionate in pregnant women. Therefore, DYMISTA Nasal Spray should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus (see TOXICOLOGY) particularly during the first trimester of pregnancy.

Like other glucocorticosteroids, fluticasone propionate is teratogenic to rodent species (see TOXICOLOGY). Adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; direct intranasal application ensures minimal systemic exposure. The relevance of these findings to humans has not yet been established.

Infants born of mothers who have received substantial doses of glucocorticosteroids during pregnancy should be carefully observed for hypoadrenalism.

Nursing Women: Glucocorticosteroids are excreted in human milk. It is unknown whether nasally administered azelastine hydrochloride/metabolites or Fluticasone propionate/metabolites are excreted in human breast milk. DYMISTA Nasal Spray should be used during lactation only if the potential benefit outweighs the potential risk to the newborns/infant (see TOXICOLOGY).

Pediatrics (<6 years of age)*:* DYMISTA is not recommended for use in children below 6 years of age as safety and efficacy have not been established in this age group.

Geriatrics (>65 years of age): Clinical trials of DYMISTA included a small number of patients 65 years of age or older. Based on the available data for DYMISTA, no adjustment of dosage of DYMISTA in geriatric patients is warranted (see DOSAGE AND ADMINISTRATION, Special Populations).

Hepatic Impairment: Formal pharmacokinetic trials using DYMISTA have not been conducted in subjects with hepatic impairment. However, systemic exposure to inhaled fluticasone furoate increased by up to 3-fold in subjects with mild, moderate and severe hepatic impairment compared with healthy subjects. Patients should be monitored for corticosteroid-related side effects (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions in controlled clinical studies with DYMISTA have been primarily associated with irritation of the nasal or throat mucous membranes, and are consistent with those expected from application of a topical medication to an already inflamed membrane. In general, adverse events (AEs) occurred with similar frequencies in patients treated with DYMISTA compared with either azelastine or fluticasone alone.

Commonly, dysgeusia, a substance-specific unpleasant taste, may be experienced after administration (often due to incorrect method of application, namely tilting the head too far backwards during administration).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults and Adolescents 12 Years of Age and Older
The clinical trial safety database for DYMISTA consists of a total of 1006 patients (97 adolescents and 909 adults) treated with DYMISTA twice per day per nostril, in four (three pivotal and one non-pivotal) 2-week, randomised, double-blind placebo-controlled studies in patients with Seasonal Allergic Rhinitis (SAR).

Treatment emergent AEs for DYMISTA and the other treatment arms were pooled across the four clinical studies.

Table 1 presents an overview of the pooled treatment emergent adverse event safety data from this pool of 2-week Phase III studies. The percentage of subjects with any AE was low in all treatment groups. Across all treatment groups, the majority of AEs were mild in nature. A total of 35 subjects withdrew due to AEs (11 subjects in the DYMISTA group and 10 subjects in the placebo group). Three subjects (2 subjects DYMISTA; 1 subject placebo) had SAEs; none of these events were considered to be related to study drug administration. The occurrence of AEs in the pooled population was generally similar to the occurrence of AEs in each individual study.

Table 1 Treatment Emergent Adverse Events with an Incidence ≥ 1.0 % in DYMISTA Treatment Group in Adults and Adolescents, by Decreasing Order of Frequency (MP4001, MP4002, MP4004, and MP4006)

Preferred term	DYMISTA N = 1006	Placebo N = 1012	AZE* N = 851	FLU** N = 846
Dysgeusia	41 (4.1)	2 (0.2)	44 (5.2)	4 (0.5)
Epistaxis	22 (2.2)	20 (2.0)	14 (1.6)	14 (1.7)
Headache	22 (2.2)	12 (1.2)	20 (2.4)	20 (2.4)

* Azelastine hydrochloride in DYMISTA vehicle
** Fluticasone propionate in DYMISTA vehicle

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 with seasonal allergic rhinitis (SAR) treated with 1 spray per nostril twice daily in one 2-week, randomized, double-blind, placebo-controlled study.

Table 2 contains the most frequently reported adverse reactions (≥ 1% in any treatment group) considered by the investigator to be potentially related to DYMISTA or placebo in the SAR controlled clinical trial.

Table 2 Treatment Related Adverse Events with an Incidence ≥ 1.0 % in any Treatment Group in Children 6-11 Years of Age, by Decreasing Order of Frequency (MP4008)

Preferred Term	DYMISTA N=152	Placebo N=152
Dysgeusia	6 (3.9%)	0 (0.0%)
Epistaxis	6 (3.9%)	3 (2.0%)

Less Common Clinical Trial Adverse Drug Reactions (<1.0%)

This section includes additional adverse events from the pooled data of the 4 placebo-controlled studies in adults and adolescents, and from the placebo-controlled study in children 6-11 years of age, that

- were reported by at least 1 patient using DYMISTA and considered by the investigator to be potentially related to the study drug, or
- were reported by at least 3 patients using DYMISTA and occurred at a greater incidence than placebo.

Ear and labyrinth disorders: Tinnitus
Eye disorders: Eye irritation
Gastrointestinal disorders: Dry mouth, Nausea, Abdominal discomfort, Abdominal pain upper, Vomiting
General disorders and administration site conditions: Mucosal erosion, Fatigue, Product taste abnormal, Mucosal ulceration
Infections and infestations: Upper respiratory tract infection, Acute sinusitis, Laryngitis, Pharyngitis, Viral upper respiratory tract infection
Metabolism and nutrition disorders: Polydipsia
Nervous systems disorders: Somnolence, Dizziness, Hypogeusia, Lethargy, Parosmia
Psychiatric disorders: Disorientation
Respiratory, thoracic and mediastinal disorders: Nasal discomfort, Cough, Oropharyngeal pain, Sneezing, Throat irritation, Nasal dryness, Rhinalgia, Rhinorrhoea, Upper-airway cough syndrome, Dry throat, Nasal congestion, Nasal mucosal disorder, Nasal septum ulceration
Skin and subcutaneous tissue disorders: Dry skin, Pruritus, Rash papular

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

In the 12-month, open-label, active-controlled, long-term safety trial, 404 patients (28 adolescents and 376 adults) with perennial allergic rhinitis (PAR) or vasomotor rhinitis were treated with DYMISTA Nasal Spray 1 spray per nostril twice daily and 207 patients were treated with fluticasone propionate nasal spray, 2 sprays per nostril once daily. Overall, at least one treatment-emergent adverse event was mentioned by 47% of the subjects in the DYMISTA Nasal Spray treatment group and 44% of the subjects in the fluticasone propionate nasal spray group. At least one adverse event that was considered by the investigator to be potentially related to the study drug was reported by 9% of the subjects in the DYMISTA Nasal Spray treatment group and 11% of the subjects in the fluticasone propionate nasal spray group. The most frequently reported treatment-emergent adverse events (≥ 2%) with DYMISTA Nasal Spray were headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhea, and epistaxis. Of these adverse events the investigator considered headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia and

epistaxis as potentially related to the study drug. In the DYMISTA Nasal Spray 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 (2.7%) treated with DYMISTA Nasal Spray and 6 of 207 patients (2.9%) 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 safety trial in pediatric patients 6-11 years of age, 264 patients with allergic rhinitis (AR) were treated with DYMISTA, 1 spray per nostril twice daily and 89 patients were treated with fluticasone propionate nasal spray, 1 spray per nostril twice daily. Overall, treatment-emergent adverse events were 40% in the DYMISTA treatment group and 36% in the fluticasone propionate nasal spray group. The most frequently reported treatment-emergent adverse events (≥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.

Post-Market Adverse Drug Reactions

In addition to adverse drug reactions reported from clinical trials, the following reactions have been identified from post-market experiences with DYMISTA (frequencies cannot be estimated):
Ear and labyrinth disorders: vertigo
Cardiac disorders: palpitations
Eye disorders: vision blurred
Gastrointestinal disorders: diarrhoea
General disorders and administration site conditions: chest pain, pain, therapeutic response unexpected
Immune system disorders: hypersensitivity
Investigations: drug screen false positive, heart rate increased, weight decreased
Nervous systems disorders: burning sensation, anosmia, ageusia, sedation
Psychiatric disorders: anxiety, initial insomnia, restlessness, thinking abnormal, psychomotor hyperactivity, depression
Respiratory, thoracic and mediastinal disorders: nasal septum perforation, dyspnoea, nasal obstruction, nasal ulcers
Skin and subcutaneous tissue disorders: rash, swelling face, urticaria

DRUG INTERACTIONS

Overview

Specific pharmacokinetic drug interaction studies have not been performed with DYMISTA. The drug interactions of the combination are expected to reflect those of the individual components.

The following section outlines the interactions observed with the individual components of DYMISTA.

Cytochrome P450 Inhibitors
A drug interaction study of intranasal fluticasone propionate in healthy subjects has shown that ritonavir (a highly potent CYP 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects. Co-treatment with other CYP 3A4 inhibitors, including cobicistat-containing products, is also expected to increase the risk of systemic side-effects. Therefore, concomitant use of DYMISTA and strong CYP 3A4 inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

This study has shown that other inhibitors of CYP 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. However, there have been a few case reports during worldwide post-market use of adrenal cortisol suppression associated with concomitant use of azole anti-fungals and inhaled fluticasone propionate. Therefore, care is advised when coadministering potent CYP 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

Central Nervous System Depressants
Concurrent use of DYMISTA Nasal Spray 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).

Drug-Drug Interactions

Table 3: Established or Potential Drug-Drug Interactions

Drug type	Ref	Effect	Clinical comment
Ritonavir Cobicistat	CT, PM	Systemic effects including Cushing's syndrome and adrenal suppression.	Concomitant use of fluticasone propionate and ritonavir or cobicistat-containing products should be avoided. (See DRUG INTERACTIONS: Overview)
Ketoconazole	CT PM	Minor increased systemic exposure to fluticasone propionate.	Care is advised when co-administering ketoconazole (See DRUG INTERACTIONS: Overview)
Acetylsalicylic acid	T		Use with caution in conjunction with corticosteroids in hypoprothrombinemia.
Cimetidine	CT	After oral administration of 4.4 mg azelastine hydrochloride twice daily, cimetidine has been shown to increase the plasma levels of azelastine. This is thought to be due to cimetidine inhibiting the metabolism of azelastine by interacting with the hepatic cytochrome P450 system.	Care is advised when co-administering cimetidine.

		No interaction was seen following co-treatment with ranitidine.	

CT = Clinical Trial; PM = Post-marketing; T = Theoretical

Drug-Lifestyle Interactions

In clinical trials, the occurrence of somnolence has been reported in some patients (0.7% of patients) taking DYMISTA (see ADVERSE REACTIONS). In isolated cases fatigue, weariness, exhaustion, dizziness or weakness that may also be caused by the disease itself, may occur when using DYMISTA Nasal Spray. In these cases, the ability to drive and use machines may be impaired. Alcohol and other central nervous system depressants may enhance this effect and should be avoided.

DOSAGE AND ADMINISTRATION

Dosing Considerations

A relief of nasal allergic symptoms is observed within 30-45 minutes after administration of DYMISTA. However, since the full effect of DYMISTA depends on its regular use, patients must be instructed to take the nasal inhalation at regular intervals.

Recommended Dose and Dosage Adjustment

Adults, Adolescents, and Children (6 Years of Age and Older): The recommended dose of DYMISTA is one actuation in each nostril twice daily (morning and evening).

Special Populations

Pregnant Women

DYMISTA Nasal Spray should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus particularly during the first trimester of pregnancy (see WARNINGS AND PRECAUTIONS, Special Populations and TOXICOLOGY).

Nursing Women

DYMISTA Nasal Spray should be used during lactation only if the potential benefit outweighs the potential risk to the newborns/infant (see WARNINGS AND PRECAUTIONS, Special Populations and TOXICOLOGY).

Geriatrics

Based on the available data for DYMISTA, no adjustment of dosage of DYMISTA in geriatric patients is warranted (see WARNINGS AND PRECAUTIONS, Special Populations). 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.

Children less than 6 Years

DYMISTA Nasal Spray is not recommended for use in children less than 6 years of age as safety and efficacy have not been established in this age group.

Hepatic impairment
No dosage adjustment is required for patients with hepatic impairment. Formal pharmacokinetic trials using DYMISTA Nasal Spray have not been conducted in subjects with hepatic impairment. Since fluticasone propionate is predominantly cleared by hepatic metabolism, caution should be exercised when dosing patients with hepatic impairment as they may be more at risk of systemic adverse reactions associated with corticosteroids. Therefore, patients with hepatic disease should be closely monitored. (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Renal or cardiac impairment
No specific studies in patients with renal or cardiac impairment were conducted.

Missed Dose
If a single dose is missed, the next dose should be taken when it is due. A double dose should not be taken at the same time.

Administration
DYMISTA is for administration by the nasal route only. Contact with the eyes should be avoided.

The patients should be advised that the bottle should be shaken gently before use until no residue is observed at the bottom of the bottle and the protective cap be removed afterwards. Prior to first use DYMISTA must be primed by pressing down and releasing the pump 6 times away from the face. If DYMISTA has not been used for more than 7 days it must be re-primed by pressing down and releasing the pump a sufficient number of times until a fine mist is produced.

After each use, the patient should wipe the spray tip with a clean tissue or cloth and then replace the protective cap.

OVERDOSAGE

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

Azelastine hydrochloride:
In the event of overdose after incidental oral uptake, disturbances of the central nervous system (including drowsiness, confusion, coma, tachycardia and hypotension) caused by azelastine hydrochloride are to be expected based on the results of animal experiments. General supportive measures should be employed if overdosage occurs.

There is no known antidote to DYMISTA Nasal Spray. Oral ingestion of antihistamines has the potential to cause serious adverse effects in children. Accordingly, DYMISTA Nasal Spray should be kept out of the reach of children.

Fluticasone propionate:
Intranasal administration of 2 milligrams fluticasone propionate (10 times the recommended daily dose) twice daily for seven days to healthy human volunteers has no effect on hypothalamo-pituitary-adrenal (HPA) axis function.

However, when used chronically in excessive doses or in conjunction with other corticosteroid formulations, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of fluticasone propionate should be discontinued slowly, consistent with accepted procedures for discontinuation of chronic steroid therapy (see DOSAGE AND ADMINISTRATION).

The restoration of HPA axis function may be slow. During periods of pronounced physical stress (i.e. severe infections, trauma, surgery) a supplement with systemic steroids may be advisable.

Treatment of these disorders must be symptomatic. Depending on the amount swallowed, gastric lavage is recommended. There is no known antidote to DYMISTA Nasal Spray.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
DYMISTA contains azelastine hydrochloride and fluticasone propionate, which have different modes of action in terms of improvement of allergic rhinitis and rhino-conjunctivitis symptoms.

Fluticasone propionate
Fluticasone propionate is a synthetic trifluorinated corticosteroid that possesses a high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action, e.g. 3-5 fold more potent than dexamethasone in cloned human glucocorticoid receptor binding and gene expression assays. 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.

Azelastine hydrochloride
Azelastine, a phthalazinone derivative is classified as a potent long-acting anti-allergic compound with selective H1-antagonist , mast cell stabilizing and anti-inflammatory properties. Data from *in vivo* (preclinical) and *in vitro* studies show that azelastine inhibits the synthesis or release of the chemical mediators known to be involved in early and late stage allergic reactions, e.g. leukotrienes, histamine, platelet-activating factor (PAF) and serotonin. Azelastine hydrochloride in DYMISTA Nasal Spray 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 H1-receptor antagonist activity.

Pharmacodynamics

In the dose range recommended for nasal application, neither Azelastine Hydrochloride nor Fluticasone Propionate is expected to cause relevant pharmacodynamic interactions **(**see DETAILED PHARMACOLOGY).

Pharmacokinetics

Absorption

After intranasal administration of two sprays per nostril (548 µg of azelastine hydrochloride and 200 µg 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.hr/mL for azelastine and 97.7 ± 43.1 pg.hr/mL 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.

Direct absorption of fluticasone propionate in the nose is negligible due to the low aqueous solubility with the majority of the dose being eventually swallowed. When administered orally the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

There was no evidence of pharmacokinetic interactions between azelastine hydrochloride and fluticasone propionate. However, fluticasone systemic exposure was ~50% increased when compared with a marketed fluticasone nasal spray. The absolute systemic serum concentration is still very low as typical for fluticasone propionate intranasal administration with mean peak concentration (C_{max}) of approximately 10 pg/mL. DYMISTA Nasal Spray was equivalent to a marketed azelastine nasal spray with respect to azelastine systemic exposure.

Distribution

Fluticasone propionate has a large volume of distribution at steady-state (approximately 318 litres). Plasma protein binding is 91%.

The volume of distribution of azelastine is high indicating distribution predominantly into the peripheral tissue. The level of protein binding is 80-90%. Additionally, both drugs have broad therapeutic windows. Therefore, drug displacement reactions are unlikely.

Metabolism

Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Care should be taken when co-administering potent CYP3A4 inhibitors such as ketoconazole and ritonavir as there is potential for increased systemic exposure to fluticasone propionate (see DRUG INTERACTIONS AND WARNINGS AND PRECAUTIONS).

Azelastine is metabolized to *N*-desmethylazelastine via by the cytochrome P450 enzyme system. The specific P450 isoforms responsible for the biotransformation of azelastine have not been identified.

Elimination
The elimination rate of intravenous administered fluticasone propionate is linear over the 250-1000 microgram dose range and are characterised by a high plasma clearance (CL=1.1 l/min). The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile.

Plasma elimination half-lives after a single dose of azelastine are approximately 20-25 hours for azelastine and about 45 hours for the therapeutically active metabolite N-desmethyl azelastine. Excretion occurs mainly via the feces.

Special Populations and Conditions
The pharmacokinetic properties of DYMISTA Nasal Spray have not been assessed in special populations and no gender specific data have been obtained.

However, no significant difference was found in $t_{½}$, C_{max} or AUC in an oral single dose study of 4 mg azelastine in 6 patients with hepatic impairment compared to normal subjects. Caution is warranted in extrapolating these data to long - term use.

In a single oral dose study of 4 mg azelastine in 9 patients, renal insufficiency (creatinine clearance <50 mL/min) resulted in a 70-75% higher C_{max} and AUC compared to healthy subjects. However, the number of patients evaluated in this study is too small to draw meaningful conclusions. No information regarding the use of azelastine nasal spray in renally impaired patients is available. Time to maximum concentration was unchanged.

STORAGE AND STABILITY

Store between 15 and 30°C. Do not freeze or refrigerate.

SPECIAL HANDLING INSTRUCTIONS

The bottle should be discarded after 28 or 120 sprays following priming. If more than 6 months have elapsed since the bottle was first used, it should be discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DYMISTA is a white, homogeneous, redispersible suspension intended for intranasal administration containing 0.1% (w/w) azelastine hydrochloride and 0.037% (w/w) fluticasone propionate as the active ingredients and the following non-medicinal ingredients: benzalkonium chloride, carmellose sodium, disodium edetate, glycerol, microcrystalline cellulose, phenylethyl alcohol, polysorbate 80 and purified water.

DYMISTA is available in one strength. After priming, each metered spray/actuation delivers a mean volume of 0.137 mL containing 137 mcg of azelastine hydrochloride and 50 mcg of

fluticasone propionate. The drug product is filled into Type I amber glass bottles of different sizes:

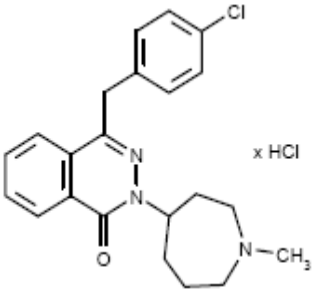
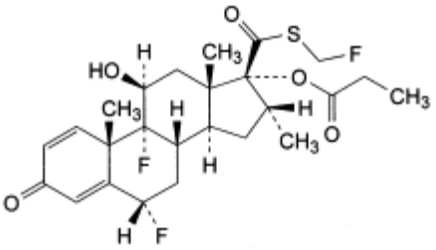
- Bottles of 25 mL are filled with 23.0g of the drug product and contain at least 120 actuations.
- Bottles of 10 mL are filled with 6.4g of the drug product and contain at least 28 actuations.

Each bottle is fitted with a spray pump, a nasal applicator and a dust cap.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance: azelastine hydrochloride and fluticasone propionate

Proper name:	azelastine hydrochloride	fluticasone propionate
Chemical name:	- D,L-4-(p-Chlorobenzyl)-2-(*N*-methyl-perhydro-azepin-4-yl)-1(2*H*)-phthalazinone hydrochloride - 4-(4-Chlorobenzyl)-2-[(4*RS*)-1-methylhexahydro-1*H*-azepin-4-yl]phthalazin-1(2*H*)-one hydrochloride - (R,S)-4[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-phthalazin-1(2H)-one hydrochloride	6α,9-Difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanaote
Molecular formula:	$C_{22}H_{24}ClN_3O \cdot HCl$	$C_{25}H_{31}F_3O_5S$
Molecular mass:	418.37 g mol^{-1}	500.6 g mol^{-1}
Structural formula:		
Physicochemical properties:	Odourless, white or almost white crystalline powder. Soluble in water: 13 g/l (25°C), soluble in ethanol and methylene chloride. Azelastine Hydrochloride is a racemic mixture. Azelastine Hydrochloride is slightly hygroscopic.	Fluticasone propionate is a white to off-white powder. Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol.

CLINICAL TRIALS

Use in Adolescents and Adults

Study Demographics and Trial Design:

Table 4: Summary of patient demographics for pivotal clinical trials

Study #	Trial design /Duration	Dosage, route of administration and duration /Study Drug and Comparators	Study subjects (n=number)	Mean age (Range)	Gender
MP4002	Randomized, Double Blind, Parallel Group, Multicentre 14 days	One spray per nostril twice daily 1) DYMISTA® 2) Azelastine 3) Fluticasone propionate 4) Placebo	831 subjects with SAR	36.2 - 38.6 (12-77) years	300M/531F
MP4004	Randomized, Double Blind, Parallel Group, Multicentre 14 days	One spray per nostril twice daily 1) DYMISTA® 2) Azelastine 3) Fluticasone propionate 4) Placebo	776 subjects with SAR	37.0 - 38.8 (12-77) years	282M/494F
MP4006	Randomized, Double Blind, Parallel Group, Multicentre 14 days	One spray per nostril twice daily 1) DYMISTA® 2) Azelastine 3) Fluticasone propionate 4) Placebo	1791 subjects with SAR	34.2 – 36.4 (12-83) years	694M/1097F

Study results

The efficacy and safety of DYMISTA in seasonal allergic rhinitis was evaluated in 3 pivotal randomized, multicenter, double-blind, placebo-controlled clinical trials in 760 adult (18-78 years) and 88 adolescent (12-17 years) patients with seasonal allergic rhinitis. The population of the trials was 64% female, 36% male; 80% white, 16% black, 2% Asian, 1% other.

Patients with moderate to severe nasal symptoms 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 Nasal Spray and are not commercially marketed.

Safety and efficacy of DYMISTA was further assessed in a 12 month study (MP4000) in patients with chronic allergic or vasomotor rhinitis. One further study (3311) was performed to assess the

onset of action of DYMISTA using a standardized Environmental Exposure Chamber (EEC) model.

During the pivotal studies, nasal symptoms of itchy nose, nasal congestion, runny nose and sneezing, and ocular symptoms of itchy eyes, watery eyes, and eye redness were rated twice daily in a diary, using a 4-point scale from 0 (no symptoms) to 3 (severe symptoms). The scores were summed up to a total nasal symptom score (TNSS) and a total ocular symptom score (TOSS), respectively.

Reflective Total Nasal Symptom Score (rTNSS)
The primary endpoint for these studies was the change from baseline in the combined (daytime plus nighttime) 12-hour reflective total nasal symptom score (crTNSS: maximum possible score of 24) over the 14-day study period vs. placebo, azelastine or fluticasone propionate alone.

Table 5 below shows the primary efficacy results for the individual pivotal studies expressed as absolute change in crTNSS compared with placebo and all active treatments. In each study DYMISTA was statistically and clinically significantly superior to placebo and the monotherapy components (azelastine alone and fluticasone alone). Furthermore, each active substance contributes to the treatment effect of the combination DYMISTA. A statistically significant decrease in TNSS, as compared to placebo, was seen 30-45 minutes after the first dose in subjects who received DYMISTA.

Table 5 Combined 12-Hour rTNSS, AM and PM Combined, Adults and Adolescents, (ITT Population) – Least Square Means and 95% Confidence Intervals for Pairwise Differences

Study No.	Parameters	DYMISTA	FLU*	AZE**	PLA^
MP4002	N	207	207	208	209
	LS mean BL	18.3	18.2	18.3	18.6
	LS mean (SD) overall change from BL	-5.6 (5.2)	-4.7 (4.7)	-4.2 (4.6)	-2.9 (3.9)
	P-values (ANCOVA) vs. DYMISTA	-	0.034	0.001	< 0.001
MP4004	N	193	188	193	199
	LS mean BL	18.3	18.6	18.5	18.2
	LS mean (SD) overall change from BL	-5.5 (5.2)	-4.6 (5.1)	-4.5 (4.6)	-3.0 (3.9)
	P-values (ANCOVA) vs.DYMISTA	-	0.038	0.032	< 0.001
MP4006	N	448	450	443	448
	LS mean BL	19.3	19.4	19.5	19.4
	LS mean (SD) overall change from BL	-5.5 (5.2)	-4.9 (4.7)	-4.8 (4.8)	-3.4 (4.3)
	P-values (ANCOVA) vs. DYMISTA	-	0.029	0.016	< 0.001

* Fluticasone propionate in DYMISTA vehicle
** Azelastine hydrochloride in DYMISTA vehicle
^ DYMISTA vehicle
BL Baseline
SD Standard Deviation
ITT Intent To Treat

Reflective Total Ocular Symptom Score (rTOSS)
The change from baseline in combined (daytime plus nighttime) AM+PM rTOSS was included as secondary efficacy endpoint in the pivotal studies (key secondary efficacy endpoint in studies MP4004 and MP4006). Results for the individual pivotal studies are presented in Table 6 below. Across all studies, DYMISTA was statistically and clinically significantly superior to placebo. In

1 of 3 studies DYMISTA was also statistically and clinically significantly superior to fluticasone propionate. DYMISTA was numerically superior to azelastine hydrochloride.

Table 6 Combined 12-Hour rTOSS, AM and PM Combined, Adults and Adolescents, (ITT Population) – Least Square Means and 95% Confidence Intervals for Pairwise Differences

Study No.	Parameters	DYMISTA	FLU*	AZE**	PLA^
MP4002	N	207	207	208	209
	LS mean BL	11.9	11.4	11.5	12.1
	LS mean (SD) overall change from BL	-3.1 (4.0)	-2.6 (3.5)	-2.8 (3.8)	-1.9 (3.3)
	P-values (ANCOVA) vs. DYMISTA	-	0.097	0.457	<0.001
MP4004	N	193	188	193	199
	LS mean BL	11.7	12.0	11.8	11.6
	LS mean (SD) overall change from BL	-3.6 (3.9)	-2.7 (3.6)	-3.0 (3.3)	-2.0 (3.1)
	P-values (ANCOVA) vs.DYMISTA	-	0.009	0.069	<0.001
MP4006	N	448	450	443	448
	LS mean BL	12.3	12.3	12.4	12.2
	LS mean (SD) overall change from BL	-3.0 (4.0)	-2.8 (3.5)	-3.0 (3.8)	-2.0 (3.5)
	P-values (ANCOVA) vs. DYMISTA	-	0.247	0.912	<0.001

* Fluticasone propionate in DYMISTA vehicle
** Azelastine hydrochloride in DYMISTA vehicle
^ DYMISTA vehicle
BL Baseline
SD Standard Deviation
ITT Intent To Treat

DYMISTA also improved individual nasal and ocular symptoms, postnasal drip and the patients' disease-related quality of life (Rhinoconjunctivitis Quality of Life Questionnaire – RQLQ) as compared to placebo in all 3 pivotal studies.

Onset of Action

Pivotal trials showed that under clinical conditions DYMISTA becomes efficacious within the first 30-45 minutes. From chamber studies with azelastine, the onset of action was observed at 15 minutes after administration (efficacy at time points earlier than 15 minutes was not assessed). In a chamber study with DYMISTA, statistically significant relief of nasal allergic rhinitis symptoms was observed at the earliest time point assessed, 5 minutes after administration of DYMISTA. In a responder analysis, the median time to a 50% reduction in nasal symptoms was approximately 30 minutes. A statistically significant relief of ocular symptoms was observed by 10 minutes after administration of DYMISTA.

Use in 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 (MP4008). 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. The change from baseline in combined AM+PM rTOSS was included as a secondary efficacy endpoint. Symptoms were

assessed by the subject or by the caregiver. Results of the original analyses were numerically supportive, but did not achieve statistical significance. The post hoc analyses showed greater treatment differences between DYMISTA and placebo with increasing degree of child self-rating. When the children assessed symptom severity by themselves (self-rating >90%), children treated with DYMISTA were reported to have experienced better relief than those treated with placebo (Table 7). Self-rating occurred most frequently in the older children, aged 9 – 11 years.

Table 7: Combined 12-Hour rTNSS and rTOSS, AM and PM, Children 6-11 Years, (ITT Population) – Least Square Means for Pairwise Differences (MP4008)

	rTNSS			rTOSS	
	DYMISTA – PLA^	**95% CI**	**P value**	**DYMISTA – PLA^**	**95% CI**
All children (n = 304)	-0.80	-1.75, +0.15	0.099	-0.53	-1.23, +0.18
Child self-rating <10% (n = 157)	-0.29	-1.65, +1.07		-0.19	-1.12, +0.74
Child self-rating 10-90% (n = 65)	-1.14	-3.02, +0.73		-0.48	-1.80, +0.84
Child self-rating >90% (n = 82)	-2.18	-3.54, -0.82		-1.34	-2.34, -0.34

^ DYMISTA vehicle
CI Confidence Interval
ITT Intent To Treat

In the per protocol population, which excluded subjects primarily non-compliant with dosing or electronic diary completion, a numerically greater difference in the LS mean change in rTNSS of -3.99 in the DYMISTA group compared to the placebo group (-2.78) was observed (difference= -1.21).

DETAILED PHARMACOLOGY

HUMAN PHARMACOLOGY

Pharmacodynamics: Fluticasone propionate is a synthetic trifluorinated glucocorticosteroid which has potent anti-inflammatory activity by acting via the glucocorticoid receptor. Fluticasone propionate was 3-fold to 5-fold more potent than dexamethasone in cloned human glucocorticoid receptor system binding and gene expression assays. When used at up to four times the recommended daily dose on the nasal mucosa, fluticasone propionate has no detectable systemic activity and causes little or no hypothalamic pituitary adrenal (HPA) axis suppression. Following intranasal dosing of fluticasone propionate, (200 mcg/day) no significant change in 24 h serum cortisol AUC was found compared to placebo (ratio 1.01, 90%CI 0.9-1.14). In the recommended dosing scheme intranasal fluticasone propionate formulations are regarded to be devoid of systemic glucocorticoid actions.

Azelastine, a phthalazinone derivative is classified as a potent long-acting anti-allergic compound with selective H_1-antagonist , mast cell stabilizing and anti-inflammatory properties. Azelastine blocks histamine release from human basophils.

Pharmacokinetics: See ACTION AND CLINICAL PHARMACOLOGY.

ANIMAL PHARMACOLOGY

Fluticasone propionate: Topical instillation of fluticasone propionate (10 mcg/animal) significantly inhibited sneezing and nasal rubbing after antigen challenge in actively sensitized rats. By contrast, in a guinea pig model of AR, treatment with topical fluticasone propionate (10 mcg/nostril) had no effect on sneezing or rubbing. However, it caused complete inhibition of nasal congestion and also suppressed IL-4 level in nasal lavage and inflammatory cell recruitment to nasal mucosa. Similarly, fluticasone propionate suppressed nasal congestion in Brown Norway rats. Fluticasone propionate significantly reduced nasal symptoms such as sneezing and rubbing in actively sensitized guinea pigs when administered for four days prior to challenge.

Azelastine Hydrochloride: The antiallergic (anti-rhinitic) activities of azelastine were evaluated in rats and guinea pigs. Azelastine inhibited the allergen challenge-evoked increase in microvascular leakage following topical, i.v. or i.m. administration. In actively sensitized guinea pigs, orally administered azelastine significantly inhibited nasal symptoms (sneezing, nasal rubbing).

TOXICOLOGY

Fluticasone Propionate

Species	Route of Administration	No. of Animals / Sex/ Group	Dose	Duration of Treatment	Observations
Acute toxicity					
Mice	Oral			Single dose	LD_{50} > 1000 mg/kg
	Subcutaneous			Single dose	
Rats	Oral			Single dose	LD_{50} > 1000 mg/kg
	Subcutaneous			Single dose	
	Intravenous			Single dose	LD_{50} > 2.0 mg/kg
	Inhalation			Single dose	LD_{50} > 1.66 mg/kg
Dogs	Inhalation			Single dose	LD_{50} > 0.82 mg/kg
Chronic Toxicity					

Rats	Inhalation		80 µg/kg/day	6 months	No changes or irritations in the respiratory tract.
	Inhalation		57 µg/kg/day	18 months	No test article related changes in the air passages. Hematology: Increased erythrocyte and platelet count, decreased lymphocyte count Serum Chemistry: Changes in plasma proteins, transaminases and electrolytes. Urinalysis: Decreased urine volume. Histology: Lymphoid depletion, thymic and adrenal atrophy. The changes are typical of excessive application of gluticosteroids.
Dogs	Inhalation		510 µg/animal/ day	6 months	No changes or irritations in the respiratory tract
	Inhalation		50.7 µg/animal/ day	12 months	No substance-related topical effects in the respiratory tract Hematology: Increased erythrocyte and platelet count, decreased lymphocyte count Serum chemistry: Decrease of urea, creatinine and glucose, increase of protein, albumin, cholesterol and sodium Histology: Thymic involution, adrenal atrophy, lymphoid depletion in lymph nodes and spleen, glycogenic infiltration of the liver Test article related findings corresponded with effects known during therapy with glucocorticosteroids.
Mutagenicity					
Fluticasone propionate did not induce gene mutation in prokaryotic and eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test.					
Carcinogenicity					
Mice	Oral		1000 µg/kg/day	18 months	No tumorigenic potential.

Rats	Inhalation		57 µg/kg/day	2 years	No indication of substance related carcinogenic potential.
Reproduction and Teratology					
Reproduction and fertility					
Rats	Subcutaneous		50 µg/kg/day		No evidence of impairment of fertility in males and females.
Embryo and fetal development					
Mice	Subcutaneous		150 µg/kg/day		Fetal toxicity characteristic of potent corticosteroid compounds including retarded ossification and cleft palates, in presence of maternal toxicity (reduction of body weight).
Rats	Subcutaneous		30 µg/kg/day to 100 µg/kg/day		Doses from 30 µg/kg onwards caused maternal toxic effects. Following the maximum dose of 100 µg/kg the body weights of foetuses were reduced and the ossification retarded.
Rabbits	Subcutaneous		4 µg/kg/day		Fetal weight reduction and cleft palate.
	Oral		300 µg/kg/day		No teratogenic effects.
Peri-and postnatal toxicity					
Rats	Subcutaneous		15 µg/kg/day to 50 µg/kg/day		No influence.
Local Tolerance					
Cynomolgus monkeys	Intranasal		400 µg/animal/ day	28 days	No local irritancy to the nasal cavity or respiratory tract, or systemic toxicity.
Rabbit	Conjunctival				Micronised fluticasone propionate was considered to be non-irritating in the rabbit eye when assessed using a modified Draize test.
Guinea pig	Dermal				Results from split adjuvant test for evaluating contact sensitivity were completely negative.

Azelastine hydrochloride

Species	Route of Administration	No. of Animals / Sex/ Group	Dose	Duration of Treatment	Observations
Acute toxicity					
Mice	Oral	7		Single dose	LD_{50} 150 mg/kg
Rats	Oral	7		Single dose	LD_{50} 600 mg/kg
Guinea Pigs	Oral	7		Single dose	LD_{50} 128mg/kg
Dogs	Oral	3		Single dose	LD_{50} 130 mg/kg
Chronic Toxicity					
Rats	Intranasal	15	0.2, 0.4 and 0.8 mg/animal/day (once, twice or 4 times daily 0.1 ml per nostril)	6 months	No mucosal irritating properties. No primary substance-related systemic-toxicological changes. No toxic effect level (NOAEL) is 0.8 mg/day/animal.
Dogs	Intranasal	4	0.42, 0.84 and 1.68 mg/animal/ day (0.14, 0.24 and 0.56 ml per nostril)	6 months	No mucosal irritating properties. No primary substance-related systemic-toxicological changes. Non-significant and slightly reduced bodyweight gain as well as a delayed onset of oestrus are considered to be secondary effects as a result of the stress associated with the treatment (bitter taste of the substance) and has no corresponding finding in other toxicity tests with higher systemic exposure. No toxic effect level (NOAEL) is 1.68 mg/day/animal.
Mutagenicity					
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.					
Carcinogenicity					
Mice	Oral	Control : 100 + 5	0,1, 5, 25 mg/kg/day	2 years	No evidence of carcinogenicity.

		Treatment: 50 + 5			
Rats	Oral	Control: 100 + 15 Treatment: 50 + 15	0, 1, 5, 30 mg/kg/day	2 years	No evidence of carcinogenicity.
Reproduction and Teratology					
Reproduction and fertility					
Rats	Oral	24 M&F (0-30 mg/kg) 12 M&F (68.6 mg/kg)	0, 0.3, 3.0, 30, 68.6 mg/kg/day	M: 77 days prior to and through mating F: 14 days prior to and throughout mating to day 7 of gestation	0.3 to 30 mg/kg: No effects on male and female fertility. 68.6 mg/kg: The duration of oestrous cycles was prolonged and copulatory activity and the number of pregnancy were decreased. The number of corpora lutea and implantations were decreased; however, pre-implantation loss was not increased.
	Oral	24 M&F	0, 0.3, 3.0, 30 mg/kg/day	M: 10 wks. prior to & during mating F: 14days prior to & during mating throughout pregnancy to day 21 pp.	0.3 to 3.0 mg/kg: No effects on male and female fertility. 30 mg/kg: Reduced fertility index.
Embryo and fetal development					
Mice	Oral	10 – 14 pregnant F	0, 0.3, 3.0, 68.6 mg/kg/day	Gestation days 6-15	0.3 to 3.0 mg/kg: Neither fetal nor maternal effects occurred. 68.6 mg/kg: Embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification and decreased fetal weight. This dose also caused maternal toxicity as evidenced by decreased body weight.
Rats	Oral	21 – 25 pregnant F	0, 0.3, 3.0, 30, 68.6 mg/kg/day	Gestation days 7 - 17	0.3-3 mg/kg: Neither fetal nor maternal effects occurred. 30 mg/kg: Malformations (oligo- and brachydactylia), delayed ossification and

					skeletal variations, in the absence of maternal toxicity. 68.6 mg/kg: Embryo-fetal death and decreased fetal weight, however this dose caused severe maternal toxicity.
Rabbits	Oral	10 – 14 pregnant F	0, 0.3, 30, 50 mg/kg/day	Gestation days 6 - 18	0.3 mg/kg: Neiher fetal nor maternal effects occurred 30-50 mg/kg: Abortion, delayed ossification and decreased fetal weight, however these doses also resulted in severe maternal toxicity.
Peri-and postnatal toxicity					
Rats	Oral	24 F	0, 0.3, 3.0, 30 mg/kg/day	Gestation day 17 to post partum day 21	0.3 to 30 mg/kg: No influence on the peri- and postnatal phase.
Local Tolerance					
Rabbits	Dermal	3 M or F	0.5 g azelastine hydrochloride in 0.8 ml aqua demin	Single application	No irritating effects on the intact skin.
	Conjunctival	5	0.1 ml of 0.1% azelastine hydrochloride solution	Instillation 5 times daily during 5 days	Assessment via the Draize key classifies azelatine-HCl as no-irritant to the mucosa.
Dogs	Conjunctival	5 F	0.1 ml of 0.1% azelastine hydrochloride solution	Instillation 5 times daily during 14 days	No adverse effects when applied topically to the eye.

Azelastine Hydrochloride and Fluticasone Propionate Combination

Species	Route of Administration	No. of Animals / Sex/ Group	Treatment	Dose	Duration of Treatment	Observations
Acute toxicity						

No tests performed						
Chronic Toxicity						
Sprague-Dawley rats	Intranasal	10	Control article Vehicle DYMISTA Azelastine hydrochloride Nasal Spray Fluticasone propionate Nasal Spray	0.1 mL per nostril twice daily	14 days	The intranasal administration of 0.1% azelastine hydrochloride /0.0365% fluticasone propionate was not considered to have any adverse effects, except for decreased body weights for the female animals which was also observed for animals administered azelastine hydrochloride or fluticasone propionate alone. A slight yet statistically significant increase in glucose and calcium values was noted for the test article-treated females.
	Intranasal	10	Control article Vehicle DYMISTA Azelastine hydrochloride Nasal Spray Fluticasone propionate Nasal Spray	0.1 mL per nostril twice daily	90 days	The overall systemic exposure to azelastine (based on AUC_{last}) on Study Day 91 was comparable to the value of Study Day 1 for both azelastine/fluticasone nasal spray and azelastine hydrochloride, indicating a lack of appreciable accumulation during twice-daily intranasal administration of both azelastine/fluticasone nasal spray and azelastine hydrochloride. The animals which received fluticasone propionate, either in combination with azelastine or alone exhibited lower body weight throughout treatment, especially in female animals. Histopathological evaluation revealed increased mast cells only in the mesenteric lymph nodes of animals which received azelastine/fluticasone or fluticasone alone. The increased mast cells were not considered to be an adverse change. Overall, the toxicity profile of azelastine/fluticasone was comparable to that of the individual components.
Beagle dogs	Intranasal	3	Control article Vehicle DYMISTA	0.1 mL per nostril	14 days	The intranasal administration of 0.1% azelastine hydrochloride /0.0365% fluticasone

			Azelastine hydrochloride Nasal Spray Fluticasone propionate Nasal Spray	twice daily		propionate did not result in any definitive test article-related toxicity.
Reproduction and Teratology						
No tests performed						
Local Tolerance						
Rats	Intranasal	10	Control article Vehicle DYMISTA Azelastine hydrochloride Nasal Spray Fluticasone propionate Nasal Spray	0.1 mL per nostril twice daily	90 days	No local irritancy to the nasal cavity or respiratory tract, or systemic toxicity.
Beagle dogs	Intranasal	3	Control article Vehicle DYMISTA Azelastine hydrochloride Nasal Spray Fluticasone propionate Nasal Spray	0.1 mL per nostril twice daily	14 days	No local irritancy to the nasal cavity or respiratory tract, or systemic toxicity.

Control article: 0.9% NaCL
Vehicle: Placebo

REFERENCES

1. Berger WE, Shah S, Lieberman P, Hadley J, Price D, Munzel U, Bhatia S(7). Long-term, randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) in subjects with chronic rhinitis. J Allergy Clin Immunol Pract. 2014 Mar-Apr;2(2):179-85.

2. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, Munzel U, Bousquet J. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J.Allergy Clin. Immunol. 2012 May;129(5):1282-1289.

3. Derendorf H., Munzel U, Petzold U, Maus J, Mascher H, Hermann R, Bousquet J. Bioavailability and Disposition of Azelastine and Fluticasone Propionate When Delivered by MP29-02 - A Novel Aqueous Nasal Spray. Br J Clin Pharmacol. 2012 Jul;74(1):125-33.

4. FLONASE Allergy Relief Product Monograph, GlaxoSmithKline Inc.

5. FLOVENT Product Monograph, GlaxoSmithKline Inc.

6. Hampel, F.C., Ratner, P.H., Van Bavel, J., Amar, N.J., Daftary, P., Wheeler, W., Sacks, H. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010 Aug;105(2):168-73.

7. Horak F, Zieglmayer UP, Zieglmayer R, Kavina A, Marschall K, Munzel U, Petzold U. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. Curr Med Res Opin. 2006 Jan;22(1):151-7.

8. Patel P, D'Andrea C, Sacks HJ. Onset of action of azelastine nasal spray compared with mometasone nasal spray and placebo in subjects with seasonal allergic rhinitis evaluated in an environmental exposure chamber. Am J Rhinol. 2007 Jul-Aug;21(4):499-503.

PART III: CONSUMER INFORMATION

PrDYMISTA®
Azelastine Hydrochloride and Fluticasone Propionate Suspension Nasal Spray

137 mcg/50 mcg per metered spray

This leaflet is part III of a three-part "Product Monograph" published when DYMISTA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DYMISTA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DYMISTA® is a prescription medicine used to treat symptoms of moderate to severe seasonal allergic rhinitis (allergy in the nose) and related eye symptoms in patients 6 years of age and older who need treatment with both azelastine hydrochloride and fluticasone propionate.

What it does:
DYMISTA helps reduce the symptoms of seasonal allergic rhinitis (inflammation of the lining of the nose), such as stuffy nose, runny nose, itching, sneezing, eye redness, itchy and watery eyes.

When it should not be used:

- if you are allergic to any of the ingredients in DYMISTA,
- if you have untreated fungal, bacterial, or tuberculosis infections of the respiratory tract.

What the medicinal ingredients are:

- azelastine hydrochloride
- fluticasone propionate

What the nonmedicinal ingredients are:
benzalkonium chloride, carmellose sodium, disodium edetate, glycerol, microcrystalline cellulose, phenylethyl alcohol, polysorbate 80 and purified water.

What dosage forms it comes in:
Suspension for metered spray: 137 micrograms of azelastine hydrochloride and 50 micrograms of fluticasone propionate per spray.

WARNINGS AND PRECAUTIONS

BEFORE you start taking DYMISTA, talk to your doctor or pharmacist if you:

- Are pregnant (or planning to become pregnant). It is not known if DYMISTA will harm your unborn baby.
- Are breastfeeding or plan to breast-feed. It is not known if DYMISTA passes into your breast milk.
- Are allergic to any other corticosteroid or medications.
- Have green or yellow discharge from the nose.
- Have eye or vision problems, such as cataracts or glaucoma (increased pressure in your eye).
- Are taking other steroid medicine by mouth or as an injection.
- Are recovering from recent nasal surgery, nasal trauma or nasal ulcers.
- Have been near someone who has chickenpox or measles.
- Have a problem with your thyroid.
- Suffer from liver disease.

You should avoid coming into contact with measles or chickenpox while taking DYMISTA. If you are exposed, tell your doctor.

Drugs like DYMISTA can cause eye disorders:

- Cataracts: clouding of the lens in the eye, blurry vision, eye pain;
- Glaucoma: an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.
- You should have regular eye exams.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. DYMISTA may affect the way other medicines work, and other medicines may affect how DYMISTA works.

In particular tell your healthcare provider before taking DYMISTA , if you are taking or have recently taken:

- ritonavir or cobicistat-containing products (commonly used to treat HIV infection or AIDS). Your healthcare provider may wish to monitor you carefully if you are taking these medicines.
- ketoconazole (for fungal infections).
- cimetidine (inhibits stomach acid production).
- Acetylsalicylic acid (ASA) and you have a blood clotting problem.

Rarely, DYMISTA can cause sleepiness or drowsiness. These

may also be caused by the disease itself. 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.

PROPER USE OF THIS MEDICATION

DYMISTA is for use in your nose only. **Do not spray it into your eyes or mouth. If you spray DYMISTA Nasal Spray into your eye(s), flush your eye(s) with large amounts of water for 10 minutes and then call your doctor.** Use DYMISTA Nasal Spray exactly as recommended by your healthcare provider.

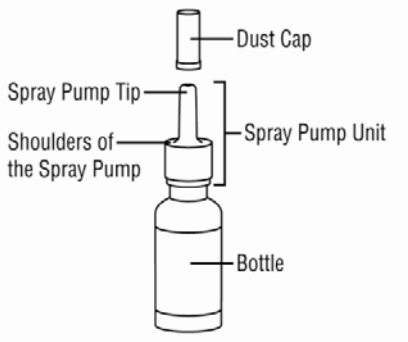
DYMISTA relieves the symptoms within 30 minutes. However, you will get the best results if you keep using DYMISTA regularly.

Do not prick the nozzle in case spray is not obtained. Clean the actuator with water.

Usual dose:
Adults and Children (6 years of age and older): 1 spray in each nostril twice a day (morning and evening).

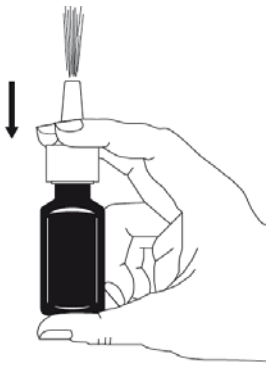
Preparing the spray
1. Shake the bottle gently until no residue is observed at the bottom of the bottle and then remove the protective cap (see Figure 1).

Figure 1



2. The first time the nasal spray is used, you must prime the pump.
- Prime the pump by putting two fingers on either side of the spray pump and place your thumb on the bottom of the bottle.
- Press down and release the pump 6 times into the air away from your face until a fine mist appears (see Figure 2).
- Now your pump is primed and ready to use.

Figure 2



3. If the nasal spray has not been used for more than 7 days, you will need to prime the pump until a fine mist appears again.

Using the spray
1. Blow your nose to clear your nostrils.

2. Keep your head tilted downwards towards your toes. **Do not tilt head backwards.**
3. Hold the bottle upright and carefully insert the spray tip into one nostril.
4. Close other nostril with your finger, rapidly press down once on the spray pump and sniff gently at the same time (see Figure 3).
5. Breathe out through your mouth.

Figure 3

6. Repeat in your other nostril.
7. Breathe in gently, and **do not tilt your head back after dosing**. This will stop the medicine going into your throat and causing an unpleasant taste (see Figure 4).

Figure 4

8. After each use wipe the spray tip with a clean tissue or cloth and then replace the protective cap.

It is important that you take your dose as advised by your doctor. You should use only as much as your doctor recommends.

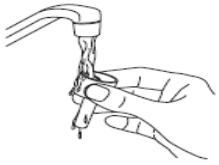
You may experience a bitter taste in your mouth, especially if you tilt your head backwards when you are using the nasal spray. This is normal. This should go away if you have a soft drink a few minutes after using this medicine. Occasionally you may sneeze a little after using this spray but this soon stops. You may experience an unpleasant smell.

To Clean the Spray Pump Tip:
Your DYMISTA Nasal Spray should be cleaned at least 1 time each week.
1. Remove the dust cap and then gently pull upward on the spray pump unit to remove it from the bottle. (See Figure 5)

Figure 5

2. Wash the spray pump unit and dust cap in warm tap water. (See Figure 6)

Figure 6



3. Allow to dry completely. When dry, place the spray pump unit and dust cap back on the bottle. (See Figure 7)

Figure 7

4. If the spray pump unit becomes blocked, it can be removed as instructed above in Step 1 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.**

5. After the spray pump unit is unblocked, rinse the applicator and cap with cold water, and allow them to dry as in Step 3 above. When dry, place the spray pump unit back on the bottle and put the dust cap on the spray pump tip.

6. Reprime the bottle as in **Preparing the spray** above. Replace the dust cap and your DYMISTA Nasal Spray is ready for use.

Overdose:
With the nasal route of administration overdose reactions are not anticipated.

If a child accidentally swallows DYMISTA Nasal Spray or you use too much DYMISTA Nasal Spray, call your doctor or go to the nearest hospital emergency room right away.

In case of accidental drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a dose, take another dose as soon as you remember but if it is near to the time for the next dose, wait until it is due. Do not take a double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, DYMISTA may cause side effects in some people. Side effects that may occur with the use of antihistamine and corticosteroid nasal sprays, including DYMISTA, are:

- headache
- change in sense of taste and/or smell
- nose bleeds
- nasal ulcers; pain, burning, irritation
- crusting in the nose
- runny nose
- soreness or dryness in the inside of the nose
- sore throat, upper respiratory tract infection
- fever, cough, stuffy nose, chills, feeling tired
- sleepiness or drowsiness

If any of these affects you severely, tell your doctor, nurse or pharmacist.

Slower growth in children (6 years of age and older) has occurred with use of corticosteroid nasal spray. Your physician should monitor your growth regularly if you are in this age group.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	**Cushing's Syndrome:** rapid weight gain especially around the body and face; excess sweating; thinning of the skin with easy bruising and dryness; muscle and bone weakness.		✓	
	Decreased Adrenal Function: tiredness, weakness, nausea and vomiting.		✓	
	Osteonecrosis: (tiny breaks in a bone leading to eventual collapse): Progressive or persistent pain or limited range of motion in a joint or limb.		✓	
	Cataracts: glare, reduced vision.		✓	
	Glaucoma: increased pressure in your eyes, eye pain.			✓
	Allergic Reactions: chest pain or tighness, wheezing, coughing or having difficulty breathing, suddenly feeling weak or lightheaded (which may lead to collapse or loss of consciousness), swelling around the face, mouth or tongue, eyes or lips with difficulty swallowing, skin rashes (hives) or redness.			✓
	Nose bleed	✓		
	Nasal Perforation: if you get a constant whistling sound when you breathe from your nose, it may be a symptom of nasal septal perforation.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Infections: if you have worsening of the symptoms of infections such as existing tuberculosis, fungal, bacterial or parasitic infections or herpes of the eye.		✓	
Unknown	**Vision Blurred**		✓	

This is not a complete list of side effects. For any unexpected effects while taking DYMISTA, *contact your doctor or pharmacist.*

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. Your medicine may harm them.

Store between 15 and 30°C. Do not freeze or refrigerate DYMISTA.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, BGP Pharma ULC at: 1-844-596-9526, **www.mylan.ca**.

This leaflet was prepared by BGP Pharma ULC, Etobicoke, Ontario M8Z 2S6

Last revised: October 3, 2019