AUSTRALIAN PRODUCT INFORMATION

DYMISTA® 125/50

(azelastine (as hydrochloride) and fluticasone propionate) nasal spray

1 NAME OF THE MEDICINE

Azelastine (as hydrochloride) and fluticasone propionate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DYMISTA 125/50 nasal spray is a fixed combination product containing the following active ingredients: azelastine hydrochloride and fluticasone propionate. Each g of suspension contains 1 mg azelastine hydrochloride and 0.365 mg fluticasone propionate. One spray (137 mg) contains 125 µg of azelastine (as the base) and 50 µg of fluticasone propionate.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

DYMISTA 125/50	a white, homogeneous and redispersible suspension. It is available as a metered-spray suspension for intranasal administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Symptomatic treatment of moderate to severe allergic rhinitis and rhino-conjunctivitis in adults and children 6 years and older where use of a combination (intranasal antihistamine and glucocorticoid) is appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults and children 6 years and older

One spray in each nostril twice daily (morning and evening).

Duration of treatment

DYMISTA 125/50 nasal spray is suitable for long-term use in adults and adolescents 12 years and older. Safety of DYMISTA 125/50 use in children aged 6 to 11 years for longer than 3 months has not been assessed (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Paediatric).

Method of administration

DYMISTA 125/50 Nasal Spray is for administration by the nasal route only.

Preparing the spray:

Shake the bottle gently before each use for about 5 seconds. Then, remove the protective cap.

Prior to first use, DYMISTA 125/50 nasal spray must be primed by pressing down and releasing the pump 6 times until a fine mist appears. If DYMISTA 125/50 nasal spray has not been used for more than 7 days, reprime by pressing down and releasing the pump a number of times until a fine mist is produced.

Using the spray:

After blowing the nose, spray the suspension once into each nostril keeping the head tilted downward. After each use, wipe the spray tip and replace the protective cap.

Paediatric

In children 6 to 11 years of age, safety of DYMISTA 125/50 beyond 3 months of use has not been assessed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use).

The safety and effectiveness of DYMISTA 125/50 in paediatric patients below the age of 6 years has not been established.

Elderly

No dose adjustment is required in this population (see Sections 5.2 PHARMACOKINETIC PROPERTIES under Special Populations – *Age* and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in the Elderly).

Renal and hepatic impairment

There are no data in patients with renal and hepatic impairment (see Sections 5.2 PHARMACOKINETIC PROPERTIES under Special Populations – *Renal Impairment* and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Renal Impairment).

Caution is required when treating patients with severe hepatic impairment (see Sections 5.2 PHARMACOKINETIC PROPERTIES under Special Populations – *Hepatic Impairment* and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Hepatic Impairment).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance(s) or to any of the excipients listed in Section 6.1 LIST OF EXCIPIENTS.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Somnolence

In clinical studies, the occurrence of somnolence has been reported in some patients taking DYMISTA 125/50 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The overall incidence of somnolence was much lower than that reported for oral antihistamines. Even so, 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 125/50 until they know how they react to the nasal spray. When administered orally in combination, azelastine hydrochloride 4.4 mg tablets and alcohol showed sedative effects. As no specific information is available with the nasal spray, caution is required if DYMISTA 125/50 is used concomitantly with alcohol or other CNS depressants (see Sections 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Central Nervous System Depressants).

Local Effects

Instances of nasal ulceration and nasal septal perforation have been reported in patients following the intranasal application of corticosteroids. There were no instances of nasal ulceration or nasal septal perforation observed in clinical studies with DYMISTA 125/50.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, surgical operation or injury to the nose or mouth should not use DYMISTA 125/50 until healing has occurred.

Local infections of the nasal airways should be appropriately treated but do not constitute a specific contraindication to treatment with DYMISTA 125/50. Candidiasis of the throat can occur in patients treated with intranasal steroids. Special care should be taken when treating patients who may be susceptible to candida infections (e.g. diabetics).

DYMISTA 125/50 contains benzalkonium chloride. Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision, increased intra-ocular pressure 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. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects

Intranasal steroid products are designed to deliver drug directly to the nasal mucosa in order to minimise overall systemic glucocorticoid exposure and side effects. Systemic effects such as HPA axis suppression, reduction of bone density and retardation of growth rate in children may occur with intranasal steroids, particularly at high doses prescribed for prolonged periods of time. If there is evidence for higher than recommended doses being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The lowest dose of fluticasone propionate nasal spray that causes suppression of the HPA axis or effects on bone mineral density or growth retardation has not yet been established. However, the systemic bioavailability of fluticasone propionate is low (estimated at 1.26% using high doses), when given as fluticasone propionate nasal spray, and this limits the potential for such systemic side effects. Measurement of serum cortisol and 24 hour urinary cortisol in the clinical studies in adults did not suggest any HPA axis suppression with recommended doses. Studies of effects on the HPA axis in children have not been conducted.

Care must be taken while transferring patients from systemic steroid treatment to DYMISTA 125/50 if there is any reason to suppose that their adrenal function is impaired.

Respiratory Conditions

In patients who have tuberculosis or untreated infections of the respiratory tract, the possible benefits of the treatment with DYMISTA 125/50 should be weighed against possible risk.

Use of Cytochrome P450 3A4 Inhibitors

Care should be taken when co-administering known, strong CYP3A4 inhibitors, e.g. ritonavir and ketoconazole, as there is potential for increased systemic exposure to fluticasone propionate (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 5.2 PHARMACOKINETIC PROPERTIES – Metabolism).

Effect on Growth

Retardation of growth rate in children may occur with intranasal steroids, particularly at high doses prescribed for prolonged periods of time (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use).

Use in Hepatic Impairment

See Section 5.2 PHARMACOKINETIC PROPERTIES under Special Populations – *Hepatic Impairment*.

Use in Renal Impairment

See Section 5.2 PHARMACOKINETIC PROPERTIES under Special Populations – *Renal Impairment*.

Use in the Elderly

See Section 5.2 PHARMACOKINETIC PROPERTIES under Special Populations – Age

Paediatric Use

Safety in children 6-11 years of age has not been studied beyond 3 months of use. DYMISTA 125/50 nasal spray is not recommended for use in children below 6 years of age as safety and efficacy has not been established in this age group.

Retardation of growth rate in children may occur with intranasal steroids, particularly at high doses prescribed for prolonged periods of time (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Effect on Growth). The growth of paediatric patients receiving nasal corticosteroids, including DYMISTA 125/50, should be monitored routinely.

Effects on Laboratory Tests

No effects are known.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been performed with DYMISTA 125/50. The drug interactions of DYMISTA 125/50 are expected to reflect those of the individual components as described below.

Central Nervous System Depressants

When administered orally in combination, azelastine hydrochloride 4.4 mg tablets and alcohol showed sedative effects. As no specific information is available with the nasal spray, caution is required if DYMISTA 125/50 is used concomitantly with alcohol or other CNS depressants (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Somnolence and 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

Cytochrome P450 Inhibitors

Under normal circumstances, very low plasma concentrations of fluticasone propionate are achieved after intranasal dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

Co-treatment with CYP3A4 inhibitors, including cobicistat-containing products is expected to increase the risk of systemic side effects. The combination 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.

Ritonavir

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 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 fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Ketoconazole

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole), as there is potential for increased systemic exposure to fluticasone propionate (see Sections 5.2 PHARMACOKINETIC PROPERTIES – Metabolism and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use of Cytochrome P450 3A4 Inhibitors).

Cimetidine

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. No interaction was seen following co-medication with ranitidine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No studies on impairment of fertility were conducted with DYMISTA 125/50. However, non-clinical studies are available for the individual active component, azelastine.

In male and female rats, azelastine at oral doses of 30 mg/kg/day and greater (resulting in plasma levels which were at least about 400 times above the plasma levels at the recommended therapeutic intranasal dose) caused a decrease in the fertility index, but in long term toxicity studies up to 2 years there were no drug-related alterations in reproductive organs either in males or in females in this species. A clinical study in 21 healthy human females using an intranasal dose of 1.12 mg/day found no effect on ovulation or sexual hormone pattern.

Use in Pregnancy

Pregnancy Category: B3

There is no or insufficient evidence of safety of DYMISTA 125/50, azelastine or fluticasone propionate in human pregnancy. No studies on the effect on embryofetal development have been conducted with azelastine/fluticasone combination. Animal reproductive studies of azelastine and fluticasone propionate in mice and rats revealed evidence of teratogenicity as well as other developmental toxic effects. However, equivalent effects have not been reported when these individual compounds have been given to humans during pregnancy. Direct intranasal application ensures minimal systemic exposure. As with other medicines, the use of DYMISTA 125/50 during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

In pregnant rats there was evidence of significant diapiacental transfer of the drug to the foetuses. Azelastine was embryo lethal and teratogenic in mice at oral doses greater than 30 mg/kg/day. In rats, azelastine was embryo-toxic at oral doses greater than 3 mg/kg/day, and teratogenicity and embryolethality were seen at doses greater than 30 mg/kg/day. In rabbits, azelastine was teratogenic at oral doses greater than 20 mg/kg/day. In pregnant rats, azelastine demonstrated no peri/ postnatal toxicity at oral doses up to 30 mg/kg/day.

In rats, the no effect doses resulted in plasma levels which were at least about 25 times above the plasma levels at the recommended therapeutic intranasal dose in humans. (The calculation of the safety factor is based on plasma levels derived from oral subchronic toxicity studies).

Reproductive toxicity studies with fluticasone propionate in mice and rats have shown the expected foetotoxic and teratogenic effects at subcutaneous doses of 100 to 150 μg /kg/day and above. As with previous compounds of this class, these effects are unlikely to be relevant to human therapy.

Use in Lactation

It is not known whether DYMISTA 125/50 is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when DYMISTA 125/50 is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of DYMISTA 125/50 by nursing mothers, based on data from the individual components, a decision should be made whether to discontinue nursing or to discontinue DYMISTA 125/50, taking into account the importance of DYMISTA 125/50 to the mother. No studies in lactating animals have been conducted with the combination azelastine/fluticasone.

It is not known if azelastine is excreted in human milk.

The excretion of fluticasone propionate into human breast milk has not been investigated. Subcutaneous administration of tritiated drug to lactating rats resulted in measurable radioactivity in both plasma and milk (levels in milk were 3-7 times plasma levels) 1-8 hours post-dosing. However plasma levels in patients following intranasal application of fluticasone propionate at recommended doses are low and the amount of fluticasone ingested by the newborn is estimated to be very small as a consequence of very low maternal plasma concentration.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to the potential occurrence of somnolence (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Somnolence), patients using DYMISTA 125/50 should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as driving or operating machinery after administration of DYMISTA 125/50 until they know how they react to the nasal spray.

Caution is required if DYMISTA 125/50 is used concomitantly with alcohol or other CNS depressants (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Somnolence and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Central Nervous System Depressants).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adults and Adolescents 12 Years of Age and Older

In the 4 placebo-controlled studies (MP4001, MP4002, MP4004 and MP4006), 1006 patients were treated with DYMISTA 125/50, 1012 with placebo, 851 with azelastine (AZE) in DYMISTA 125/50 vehicle, 846 with fluticasone propionate (FLU) in DYMISTA 125/50 vehicle, 152 with Astelin® Nasal Spray (marketed AZE), and 153 with fluticasone propionate from Roxanne Laboratories Inc. (marketed FLU). The mean duration of exposure to each of these products was about 14 days. There were no relevant differences between the treatment groups in the overall rate of premature discontinuations and also the primary reason for discontinuation.

Across all treatment groups, the percentage of subjects with any AEs was low and majority of AEs were mild in nature. The most frequently reported adverse events (AEs) were dysgeusia, epistaxis and headache. However, headache and especially epistaxis were also frequently reported under placebo. 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).

Treatment-emergent adverse events reported with an incidence of ≥ 1% in the DYMISTA 125/50 treated group, in the 4 pivotal studies, are shown in Table 1.

Table 1: Treatment-emergent adverse events with an incidence of ≥ 1% in the DYMISTA 125/50 treated group, in the 4 pivotal studies

	DYMISTA 125/50	**Placebo**	**AZE§**	**FLU§**	**AZE^{marketed}**	**FLU^{marketed}**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Safety population	1006 (100)	1012 (100)	851 (100)	846 (100)	152 (100)	153 (100)
Any adverse event	165 (16.4)	117 (11.6)	124 (14.6)	111 (13.1)	23 (15.1)	22 (14.4)
Dysgeusia	41 (4.1)	2 (0.2)	44 (5.2)	4 (0.5)	3 (2.0)	0 (0.0)
Epistaxis	22 (2.2)	20 (2.0)	14 (1.6)	14 (1.7)	4 (2.6)	6 (3.9)
Headache	22 (2.2)	12 (1.2)	20 (2.4)	20 (2.4)	2 (1.3)	6 (3.9)

AEs were coded using the MedDRA dictionary Version 13.1, shown are the preferred terms. A subject with multiple AEs was counted only once.

§ In DYMISTA 125/50 vehicle.

Table 2 listed possible adverse reactions for DYMISTA 125/50, with frequencies corresponding to:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Table 2: Possible adverse reactions of DYMISTA 125/50

Frequency System Organ Class	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders					Hypersensitivity including anaphylactic reactions, angioedema, bronchospasm	
Nervous system disorder		Headache, dysgeusia, unpleasant smell		Nervousness, taste loss	Dizziness, somnolence (drowsiness, sleepiness)	
Eye disorders*					Glaucoma, increased intraocular pressure, cataract	Blurred vision
Respiratory, thoracic and mediastinal disorders			Epistaxis, nasal discomfort (including nasal irritation, stinging, itching), sneezing, nasal dryness, cough, dry throat, throat irritation		Nasal septal perforation**, mucosal erosion	Nasal ulcers
Gastrointestinal disorders				Dry mouth	Nausea	
Skin and subcutaneous tissue disorders					Rash, pruritus, urticaria	
General disorders and administration site conditions					Fatigue (weariness, exhaustion), weakness	

*A very small number of spontaneous reports have been identified following prolonged treatment with intranasal fluticasone propionate.

**Nasal septal perforation has been reported following the use of intranasal corticosteroids.

Paediatric Patients 6-11 Years of Age

The safety data described below in children 6-11 years of age reflect exposure to DYMISTA 125/50 in 152 paediatric patients (6-11 years of age; 57% male and 43% female) with seasonal allergic rhinitis (SAR) in one 2-week, randomised, double-blind, placebo-controlled clinical trial (MP4008). Patients were treated with 1 spray per nostril of DYMISTA 125/50 or placebo, twice daily. Overall, adverse reactions were 16% in the DYMISTA 125/50 treatment group, and 12% in the placebo group. Overall, 1% of patients in both the DYMISTA 125/50 and placebo groups discontinued due to adverse reactions. Table 3 contains the most frequently reported adverse reactions (≥1% in any treatment group) considered by the investigator to be potentially related to DYMISTA 125/50 or placebo in the SAR controlled clinical trial.

Table 3. Adverse Reactions with ≥1.0% in any Treatment Group in Children 6-11 Years of Age, by Decreasing Order of Frequency (MP4008)

Preferred Term	DYMISTA 125/50 N=152	Placebo N=152
Dysgeusia	6 (3.9%)	0 (0.0%)
Epistaxis	6 (3.9%)	3 (2.0%)

Long-Term (3-Month) Safety Trial in Paediatric Patients 6-11 Years of Age (MP4007)

In the 3-month, open label, active-controlled safety trial in paediatric patients 6-11 years of age, 264 patients with allergic rhinitis (AR) with a history of SAR or perennial allergic rhinitis (PAR) were treated with DYMISTA 125/50, 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 125/50 treatment group and 36% in the fluticasone propionate nasal spray group. The most frequently reported treatment-emergent adverse events (≥2%) with DYMISTA 125/50 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 125/50 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 125/50 and 3 of 89 (3%) treated with fluticasone propionate nasal spray discontinued from the trial due to adverse events.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

DYMISTA 125/50 nasal spray contains both azelastine and fluticasone propionate; therefore, the risks associated with overdosage for the individual components apply to DYMISTA 125/50.

With the nasal route of administration, overdosage reactions to azelastine are not anticipated. To date, there has been only one report of incorrect usage: a 2 year old boy drank approximately 10 mL of azelastine nasal spray. This led to a burning sensation in the nose and mouth and to spontaneous vomiting, these events lasting 5 - 10 minutes. Pulse rate, blood pressure and respiration were normal and stable, and a normal pupil reaction was found. No tissue damage in the mouth or throat occurred. The boy recovered completely.

In the event of overdosage after accidental oral uptake, disturbances of the central nervous system (including drowsiness, confusion, coma, tachycardia and hypotension) are to be expected based on the results of animal experiments. Symptomatic and supportive treatment should be instigated as there is no known antidote.

There are no data available on the effects of acute or chronic overdosage with fluticasone propionate nasal spray. Intra-nasal administration of 2,400 μg fluticasone per day (i.e. 12 times the recommended dose) for four days to healthy human volunteers caused a small degree of suppression of adrenal steroid production.

Suppression of adrenal steroid production may give rise to typical signs and symptoms of Cushing's disease, such as buffalo hump, puffiness of face, hypertension and elevated blood glucose. If such a condition were to occur, care should be taken to wean the patient slowly off the steroid due to the probability of adrenal impairment. Recovery from impaired adrenocortical function caused by prolonged steroid therapy is usually slow and has been known to last up to 12 months.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use, corticosteroids/ fluticasone, combinations, ATC code: R01AD58.

DYMISTA 125/50 is a novel formulation of azelastine hydrochloride and fluticasone propionate. Therefore, the mechanisms of actions described below for the individual components apply to DYMISTA 125/50.

Azelastine hydrochloride, 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. The major metabolite, desmethylazelastine, also exhibits H1 – receptor antagonist activity. DYMISTA 125/50 is administered as a racemic mixture. The racemate, R- and S- enantiomers were equally potent at inhibiting eyelid histamine-induced oedema in rats, however the R-enantiomer was 2-fold less active at inhibiting eyeball histamine-induced oedema.

Azelastine nasal spray has a faster onset of action than orally administered antihistamines and nasally administered corticosteroids. A relief of nasal allergic symptoms is observed within 15 minutes after administration. Fluticasone propionate has potent anti-inflammatory activity but when used topically on the nasal mucosa at recommended doses has little or no detectable systemic activity.

Clinical Trials

Adults and Adolescents 12 Years of Age and Older

The efficacy of DYMISTA 125/50 in adults and adolescents 12 years and older was established in four randomised, double-blind, placebo-controlled studies in subjects with seasonal allergic rhinitis (SAR), namely MP4001, MP4002, MP4004, and MP4006. One further study (3311) was performed to assess the onset of action of DYMISTA 125/50 using a standardised Environmental Exposure Chamber (EEC) model.

Study MP4001 compared DYMISTA 125/50 with commercial azelastine nasal spray (Astelin® Nasal Spray) and commercial Fluticasone propionate Nasal Spray from Roxane Laboratories Inc available in the US at that time. Studies MP4002, MP4004, and MP4006 compared DYMISTA 125/50 with the single compounds in the DYMISTA 125/50 vehicle. All 4 trials had in common 4 treatment groups, the same regimen (1 spray per nostril twice daily), the same duration of treatment (2 weeks), and the same primary and almost the same secondary endpoints. These studies included male and female subjects 12 years of age or older with a minimum 2-year history of SAR.

During the study, nasal symptoms of itchy nose, nasal congestion, runny nose, 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. In addition, postnasal drip was rated on the same 4-point scale. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was completed by each subject 18 years of age or older, at the start and end of 14-day treatment (or early termination).

The primary efficacy endpoint for all four placebo-controlled studies was the change from baseline in the combined (i.e. AM and PM data added) 12-hour reflective total nasal symptom score (crTNSS) over the 14 day treatment period, tested primarily in the ITT set based on last observation. Secondary efficacy endpoints included the 12-hour AM and PM reflective TNSS, the instantaneous TNSS (iTNSS), the 12-hour reflective score for postnasal drip, the 12-hour reflective TOSS, the instantaneous TOSS, the 12-hour reflective and instantaneous individual nasal and ocular symptoms and the RQLQ score. In studies MP4002, MP4004 and MP4006, an attempt was made to evaluate the onset of action.

The pooled study population was primarily female (62.9%), white (80.3%) and between 18 and 65 years of age (87.3%).

Table 4 shows the primary efficacy results for the individual pivotal studies expressed as absolute change in crTNSS compared with placebo and all active treatments. Across the individual studies, DYMISTA 125/50 was significantly superior to placebo and the monotherapy components. In addition, each individual component was significantly superior to placebo.

Table 4: Combined 12-hour reflective total nasal symptom score (crTNSS) over the 14 day treatment period for studies MP 4001, 4002, 4004 and 4006 (ITT population)

Study No.	Parameters	DYMISTA 125/50	FLU*	AZE**	PLA^
MP4001	N	153	151	152	150
	LS mean BL	18.6	18.1	17.9	18.5
	LS mean (SD) overall change from BL	-5.3 (5.1)	-3.8 (4.8)	-3.3 (4.2)	-2.2 (4.2)
	P-values (ANCOVA) vs.DYMISTA 125/50	-	0.003	<0.001	< 0.001
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 125/50	-	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 125/50	-	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 125/50	-	0.029	0.016	< 0.001

* MP4001: Fluticasone Propionate Nasal Spray from Roxane Laboratories Inc.; Other studies: FLU in DYMISTA 125/50 vehicle
** MP4001: Astelin® Nasal Spray; Other studies: AZE in DYMISTA 125/50 vehicle
^ DYMISTA 125/50 vehicle

Data from studies MP4004 and MP4006 indicate that the onset of clinically relevant action for DYMISTA 125/50 occurs within 30 minutes after first application of the combination.

In the meta-analysis that pooled data from the 4 efficacy studies, DYMISTA 125/50 was shown to be statistically significantly superior to both azelastine and fluticasone monoproducts and all active treatments were statistically significantly superior to placebo for almost all secondary efficacy variables including the reflective TNSS confined to daytime (denominated as 12hr PM) or night time (12hr AM), the instantaneous TNSS, the reflective TOSS, post nasal drip, and all individual nasal and ocular symptom scores (all $p<0.05$) except the comparison DYMISTA 125/50 with azelastine for eye redness ($p=0.0513$). DYMISTA 125/50 at least doubled the effect of azelastine and fluticasone propionate in reducing nasal and ocular symptoms score.

The RQLQ score for DYMISTA 125/50 was significantly improved over placebo for overall score and for each individual RQLQ domain in each individual study and in the meta-analysis. Across all studies and in the meta-analysis, the treatment difference in overall score between DYMISTA 125/50 and placebo exceeded the minimum clinically significant difference of -0.50.

DYMISTA 125/50 provided substantial allergic rhinitis symptom relief (50% reduction in crTNSS) at least 3 days faster than azelastine and 6 days faster than fluticasone propionate nasal spray. The superior effect of DYMISTA 125/50 to fluticasone propionate nasal spray was maintained throughout a one-year study in patients with chronic persistent allergic rhinitis and nonallergic/vasomotor rhinitis.

In an Environmental Exposure Chamber (EEC) study (3311) relief of allergic rhinitis symptoms was observed from 5 minutes after first dose of DYMISTA 125/50 for nasal (TNSS) and 10 minutes for ocular symptoms (TOSS) ($p<0.05$).

Paediatric Patients 6-11 Years of Age

In one randomised, multi-center, double-blind, placebo-controlled trial in 304 children 6 to 11 years of age with seasonal rhinitis (MP4008), patients were randomised 1:1 to receive either one spray per nostril twice daily of DYMISTA 125/50 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 (crTNSS) 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 125/50 and placebo with increasing degree of child self-rating. When the children assessed symptom severity by themselves (self-rating >90%), children treated with DYMISTA 125/50 were reported to have experienced better relief of nasal and ocular symptoms than those treated with placebo (Table 5). Self-rating occurred most frequently in the older children, aged 9-11 years.

Table 5 Study MP4008: Combined 12-Hour reflective TNSS and TOSS, Children 6-11 Years, (ITT Population) – Least Square Means for Pairwise Differences

	crTNSS			crTOSS		
	DYMISTA 125/50 – Placebo	**95% CI**	**P value**	**DYMISTA 125/50 – Placebo**	**95% CI**	**P value**
All children (n = 304)	-0.80	-1.75, +0.15	0.099	-0.53	-1.23, +0.18	0.143
Child self-rating <10% (n = 157)	-0.29	-1.65, +1.07	0.6722	-0.19	-1.12, +0.74	0.6862
Child self-rating 10-90% (n = 65)	-1.14	-3.02, +0.73	0.2281	-0.48	-1.80, +0.84	0.4713
Child self-rating >90% (n = 82)	-2.18	-3.54, -0.82	0.0020	-1.34	-2.34, -0.34	0.0090

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 greater difference in the LS mean change in crTNSS of -3.99 in the DYMISTA 125/50 group compared to the placebo group (-2.78) was observed (difference= -1.21, p = 0.022).

5.2 PHARMACOKINETIC PROPERTIES

Two pharmacokinetic studies demonstrated that simultaneous intranasal administration of azelastine hydrochloride and fluticasone propionate with DYMISTA 125/50 does not result in altered systemic absorption of either agent.

Absorption

After intranasal administration of two sprays per nostril (500 µg of azelastine and 200 µg of fluticasone propionate) of DYMISTA 125/50 nasal spray, 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 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 (tmax) from a single dose was 0.5 hours for azelastine and 1.0 hours for fluticasone.

After intranasal administration, the systemic bioavailability of azelastine hydrochloride is approximately 40%. The absolute bioavailability of intranasal fluticasone at high doses (2,400 µg/day i.e. 12 times the recommended dose) is estimated as 1.26% (90% CI 0.85, 1.86).

Distribution

After oral and intravenous administration of azelastine, the mean volume of distribution was 14.5 L/kg. In vitro studies with human plasma indicate that the plasma protein binding of azelastine and desmethylazelastine are approximately 88% and 97%, respectively.

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

Metabolism

Azelastine is extensively metabolised, desmethylazelastine being the principal metabolite. No specific isoform of cytochrome P450 was found to be specific in the metabolism of azelastine at low concentrations (6 - 30 ng/mL) in human liver microsomes.

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. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. 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 Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use of Cytochrome P450 3A4 Inhibitors and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Excretion

Plasma elimination half-lives after a single dose of azelastine are 22 hours for azelastine and 56 hours for the therapeutically active metabolite N-desmethyl azelastine. Up to 74% of radiolabelled oral or intravenous dose is excreted in faeces and 26% in urine. Thirteen percent is excreted in urine as unchanged azelastine.

The elimination rate of intravenous administered fluticasone propionate is linear over the 250—1000 µg dose range and is characterised by a high plasma clearance (CL=1.1 L/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8 h terminal half-life. 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.

Special populations

DYMISTA 125/50 was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained. The following information is available for the individual active components, azelastine and fluticasone propionate:

Hepatic Impairment

No significant difference was found in t½, C_{max} or AUC in an oral single dose study of azelastine in 6 patients with hepatic impairment compared to normal subjects. Caution is warranted in extrapolating these data to long--term use (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Hepatic Impairment).

DYMISTA 125/50 undergoes extensive first-pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver, therefore the systemic exposure of intranasal fluticasone propionate in patients with severe liver disease is likely to be increased. This may result in a higher frequency of systemic adverse events. Caution is advised when treating these patients (see Sections 5.2 PHARMACOKINETIC PROPERTIES - Metabolism, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use of Cytochrome P450 3A4 Inhibitors and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Renal Impairment

In a single oral dose study of azelastine in 9 patients, renal insufficiency (creatinine clearance <50 mL/min) resulted in a 70-75% higher Cmax and AUC compared to normal 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Renal Impairment).

Age

A pharmacokinetic study in elderly patients (n=15) receiving oral azelastine 4.4 mg twice daily found a prolongation of the Tmax and an increase in Cmax and AUC compared to results in healthy volunteers. There have been no specific studies in the elderly with the nasal spray. In clinical and post-marketing studies of the nasal spray, no increase in the incidence of adverse reactions has been seen in elderly patients.

The pharmacokinetics of DYMISTA 125/50 has not been investigated in patients under 12 years of age.

The data for paediatric pharmacokinetics of intranasal fluticasone propionate has been shown to be consistent with adult findings.

The efficacy and safety of DYMISTA 125/50 in children under 6 years of age have not been established (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use).

Race

The effect of race has not been evaluated.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies of genotoxicity were conducted with DYMISTA 125/50. However, studies are available for the individual active components, azelastine and fluticasone propionate.

Azelastine demonstrated no genotoxic potential in standard assays for gene mutations, chromosomal damage and DNA damage.

Fluticasone propionate has no mutagenic effect in vivo or in vitro. There was no evidence of a mutagenic potential in a standard battery of mutagenicity assays.

Carcinogenicity

No studies of carcinogenicity were conducted with DYMISTA 125/50; however, studies are available for the individual active components, azelastine and fluticasone propionate.

Azelastine demonstrated no carcinogenic potential in mice and rats at dietary doses up to 25 and 30 mg/kg/day respectively.

No evidence of a tumorigenic effect was observed in either a 2 year study in rats receiving doses of fluticasone propionate up to 57 µg /kg/day by inhalation or in an 18 month study in mice receiving oral doses of fluticasone propionate up to 1 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

DYMISTA 125/50 nasal spray contains the following inactive ingredients:

- disodium edetate

- glycerol
- microcrystalline cellulose
- carmellose sodium
- polysorbate 80
- benzalkonium chloride
- phenethyl alcohol
- purified water

DYMISTA 125/50 contains the antimicrobial preservatives benzalkonium chloride and phenethyl alcohol.

6.2 INCOMPATIBILITIES

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC. Do not refrigerate. Do not freeze. Discard after 6 months of first opening the bottle.

DYMISTA 125/50 nasal spray should be kept out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

DYMISTA 125/50	Container type: Amber glass (type I) 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. Pack sizes: • 4 mL bottle containing 28 sprays • 4 mL bottle containing 28 sprays (starter pack) and • 17 mL bottle containing 120 sprays.

Some pack sizes may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 203131 – DYMISTA 125/50 azelastine (as hydrochloride) 125 microgram and fluticasone propionate 50 microgram nasal spray bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

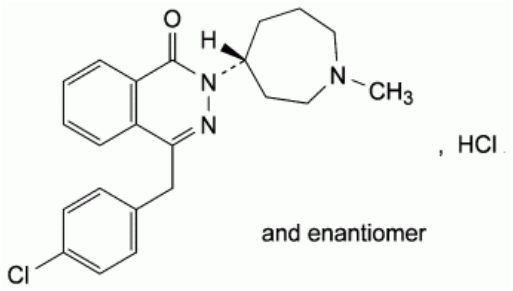
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

DYMISTA 125/50 nasal spray has a pH of 5.5 – 6.5.

Chemical Structure

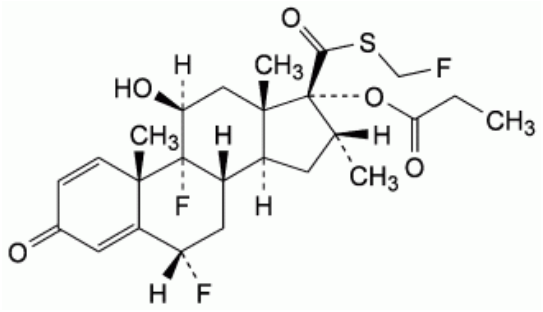
Azelastine hydrochloride



Chemical name	(*R*,*S*)-4[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-phthalazin-1(2*H*)-one hydrochloride
Molecular formula	$C_{22}H_{24}ClN_3O \cdot HCl$
Molecular weight	418.37 g mol^{-1}

Azelastine hydrochloride occurs as a white, odourless, crystalline powder with a bitter taste. It is sparingly soluble in water, and soluble in ethanol and dichloromethane. Azelastine hydrochloride is slightly hygroscopic.

Fluticasone propionate



Chemical name	6α,9-Difluoro-17-[[(fluoromethyl) sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate
Molecular formula	$C_{25}H_{31}F_3O_5S$
Molecular weight	500.6 g mol^{-1}

Fluticasone propionate is a white or almost white powder. It is practically insoluble in water, sparingly soluble in dichloromethane and slightly soluble in alcohol.

CAS Number

Azelastine hydrochloride: 79307-93-0

Fluticasone propionate: 80474-14-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

14/01/2014

10 DATE OF REVISION

05/08/2024

Summary Table of Changes

Section Changed	Summary of New Information
4.3	Add reference
4.4	Add benzalkonium warning

DYMISTA® is a Viatris company trade mark

DYMISTA_pi\Aug24/00 (CCDS 11-Dec-2023)