NEW ZEALAND DATA SHEET

DYMISTA®

1. Product Name

DYMISTA nasal spray suspension.

2. Qualitative and Quantitative Composition

DYMISTA nasal spray is a fixed combination product containing the following active ingredients: azelastine hydrochloride and fluticasone propionate.

Each gram of suspension contains 1 mg azelastine hydrochloride and 0.365 mg fluticasone propionate. One spray (137 mg) contains 125 micrograms of azelastine (as the base) and 50 micrograms of fluticasone propionate.

Excipient with known effect
One spray (137 mg) contains 14 micrograms of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

DYMISTA is formulated as a white, homogeneous and re-dispersible 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 12 years and older where use of a combination (intranasal antihistamine and glucocorticoid) is appropriate.

4.2 Dose and method of administration

Dose

Adults and adolescents (12 years and older)

One spray in each nostril twice daily (morning and evening). Do not exceed this dose.

Do not use for longer than 6 months except on the advice of a healthcare professional.

Special populations

Use in paediatric patients (below 12 years of age)

DYMISTA nasal spray is not recommended for use in children below 12 years of age as safety and efficacy has not been established in this age group.

Use in the elderly

No dose adjustment is required in this population (see section 5.2).

Use in renal and hepatic impairment

No dose adjustment is required in patients with renal impairment or mild to moderate hepatic impairment (see section 5.2).

Caution is required when treating patients with severe hepatic impairment (see section 5.2).

Method of administration

DYMISTA nasal spray is for administration by the nasal route only.

Preparing the spray

Shake the bottle gently before each use. Then, remove the protective cap.

Prior to first use, DYMISTA nasal spray must be primed by pressing down and releasing the pump 6 times until a fine mist appears. If DYMISTA 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.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Somnolence

In clinical studies, the occurrence of somnolence has been reported in some patients taking DYMISTA (see section 4.8). 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 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 is used concomitantly with alcohol or other CNS depressants (see sections 4.5 and 4.7).

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.

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 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. 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).

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 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 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 and 5.2).

Effect on growth

Retardation of growth rate in children may occur with intranasal steroids, particularly at high doses prescribed for prolonged periods of time.

Special populations

Use in paediatric patients

Safety and effectiveness of DYMISTA in paediatric patients below the age of 12 years have not been established.

Use in patients with renal impairment

See section 5.2.

Use in patients with hepatic impairment

See section 5.2.

Use in the elderly

See section 5.2.

4.5 Interaction with other medicines and other forms of interaction

No formal drug interaction studies have been performed with DYMISTA. The drug interactions of DYMISTA 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 is used concomitantly with alcohol or other CNS depressants (see sections 4.4 and 4.7).

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 corticosteroid side effects, in which 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 4.4 and 5.2).

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

Pregnancy

Category B3.
There is no or insufficient evidence of safety of DYMISTA, azelastine or fluticasone propionate in human pregnancy. No studies on the effect of embryofetal development have been conducted with azelastine/fluticasone combination. Therefore, DYMISTA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus (see section 5.3).

Breast-feeding

It is not known whether DYMISTA or its individual components are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when DYMISTA is administered to a breast-feeding woman.

DYMISTA should be used during breast-feeding only if the potential benefit to the mother justifies the potential risk to the newborns/infant (see section 5.3).

Fertility

No studies on impairment of fertility were conducted with DYMISTA. Limited data is available for the individual active component, azelastine (see section 5.3).

A clinical study in 21 healthy human females using an intranasal dose of azelastine 1.12 mg/day found no effect on ovulation or sexual hormone pattern.

4.7 Effects on ability to drive and use machines

Due to the potential occurrence of somnolence (see section 4.4), patients using DYMISTA 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 until they know how they react to the nasal spray. Caution is required if DYMISTA is used concomitantly with alcohol or other CNS depressants (see sections 4.4 and 4.5).

4.8 Undesirable effects

In the 4 placebo-controlled studies (MP4001, MP4002, MP4004 and MP4006), 1006 patients were treated with DYMISTA, 1012 with placebo, 851 with azelastine (AZE) in DYMISTA vehicle, 846 with fluticasone propionate (FLU) in DYMISTA 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 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 treated group, in the 4 pivotal studies

	DYMISTA	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 vehicle.

Table 2 listed possible adverse reactions for DYMISTA, 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

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

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

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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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 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.

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 efficacy and safety

The efficacy of DYMISTA 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 using a standardised Environmental Exposure Chamber (EEC) model.

Study MP4001 compared DYMISTA 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 with the single compounds in the DYMISTA 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 3 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 was significantly superior to placebo and the monotherapy components. In addition, each individual component was significantly superior to placebo.

Table 3: 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	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	-	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	-	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

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

In the meta-analysis that pooled data from the 4 efficacy studies, DYMISTA was shown to be statistically significantly superior to both azelastine and fluticasone mono-products 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 with azelastine for eye redness ($p=0.0513$). DYMISTA at least doubled the effect of azelastine and fluticasone propionate in reducing nasal and ocular symptoms score.

The RQLQ score for DYMISTA 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 and placebo exceeded the minimum clinically significant difference of -0.50.

DYMISTA 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 to fluticasone propionate nasal spray was maintained throughout a one-year study in patients with chronic persistent allergic rhinitis and nonallergic/vasomotor rhinitis.

In a chamber study (3311) relief of allergic rhinitis symptoms was observed from 5 minutes for nasal symptoms (TNSS) and 10 minutes for ocular symptoms (TOSS) ($p<0.05$) after administration of DYMISTA. The onset of effect was approximately two hours earlier than that observed with a free combination of intranasal fluticasone propionate and an oral antihistamine.

Paediatric population

Safety and effectiveness of DYMISTA in paediatric patients below the age of 12 years have not been established.

5.2 Pharmacokinetic properties

Two pharmacokinetic studies demonstrated that simultaneous intranasal administration of azelastine hydrochloride and fluticasone propionate with DYMISTA 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 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 (t_{max}) 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 and 4.5).

Elimination

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 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).

Dymista 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 4.4 and 4.5).

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 C_{max} 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).

Elderly

A pharmacokinetic study in elderly patients (n=15) receiving oral azelastine 4.4 mg twice daily found a prolongation of the T_{max} and an increase in C_{max} 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.

Paediatric

The efficacy and safety of DYMISTA in children under 12 years of age have not been established (see section 4.4).

5.3 Preclinical safety data

Carcinogenicity

No studies of carcinogenicity were conducted with DYMISTA. 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.

Genotoxicity

No studies of genotoxicity were conducted with DYMISTA. 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.

Fertility

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.

Development

In pregnant rats there was evidence of significant diaplacental transfer of azelastine 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.

6. Pharmaceutical Particulars

6.1 List of excipients

DYMISTA nasal spray suspension also contains:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 18 months (4 mL pack)
24 months (17 mL pack)

Opened: 6 months from first opening the bottle.

6.4 Special precautions for storage

Store at or below 25°C. Do not refrigerate and do not freeze.

For storage conditions after first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

DYMISTA nasal spray is supplied as an amber glass bottle (type I) 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 are:

- 4 mL bottle containing 28 sprays (starter pack)
- 4 mL bottle containing 28 sprays
- 17 mL bottle containing 120 sprays.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. Medicines Schedule

Pharmacy Only Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

25 May 2017

10. Date of Revision of the Text

14 November 2022

Summary Table of Changes

Section	Summary of new information
Header	Logo updated from Mylan to Viatris
6.4	Storage statement updated to “Store at or below 25°C” to align with TPDR
8	Sponsor details updated to Viatris
-	Attribution statement included for trade mark