

## DYLASTINE<sup>®</sup> 125/50

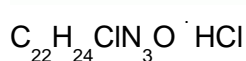
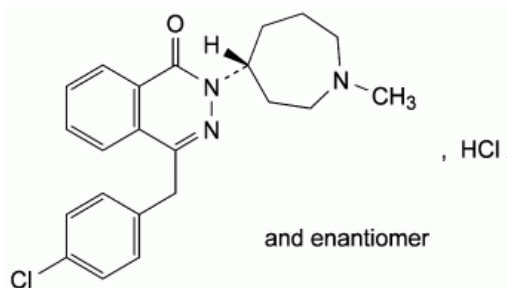
### Nasal Spray

## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Azelastine hydrochloride and fluticasone propionate

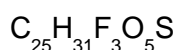
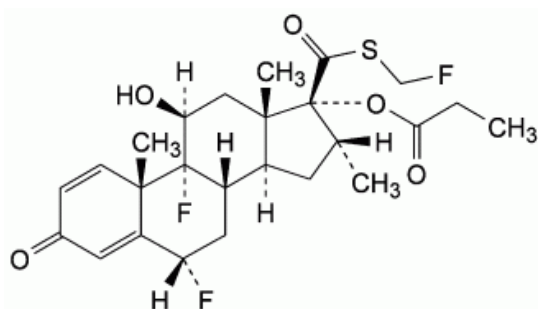
The chemical name for azelastine hydrochloride is (*R,S*)-4[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-phthalazin-1(2*H*)-one hydrochloride. Azelastine hydrochloride has the following chemical structure:



Molecular weight: 418.37 g mol<sup>-1</sup>

CAS Registry No: 79307-93-0

The chemical name for fluticasone propionate is 6 $\alpha$ ,9-Difluoro-17-[[[(fluoromethyl) sulphanyl]carbonyl]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-dien-17 $\alpha$ -yl] propanoate. Fluticasone propionate has the following chemical structure:



Molecular weight: 500.6 g mol<sup>-1</sup>

CAS Registry No: 80474-14-2

## DESCRIPTION

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

DYLASTINE 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.

DYLASTINE 125/50 nasal spray contains the following inactive ingredients: disodium edetate, glycerol, microcrystalline cellulose, carmellose sodium, polysorbate 80, benzalkonium chloride, phenethyl alcohol and purified water.

### Physical and Chemical Properties

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

## PHARMACOLOGY

### Pharmacodynamics

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

DYLASTINE 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 DYLASTINE 125/50.

Azelastine hydrochloride, a phthalazinone derivative, is classified as a potent long-acting anti-allergic compound with selective H<sub>1</sub>-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 H<sub>1</sub> – receptor antagonist activity. DYLASTINE 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.

### Pharmacokinetics

Two pharmacokinetic studies demonstrated that simultaneous intranasal administration of azelastine hydrochloride and fluticasone propionate with DYLASTINE 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 DYLASTINE 125/50 nasal spray, the mean ( $\pm$  standard deviation) peak plasma exposure ( $C_{max}$ ) was  $194.5 \pm 74.4$  pg/mL for azelastine and  $10.3 \pm 3.9$  pg/mL for fluticasone and the mean total exposure (AUC) was  $4217 \pm 2618$  pg/mL\*hr for azelastine and  $97.7 \pm 43.1$  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 **PRECAUTIONS – Use of Cytochrome P450 3A4 Inhibitors**) and **INTERACTIONS WITH OTHER MEDICINES**).

### **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**

DYLASTINE 125/50 was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained. The following data are available for the individual active component, azelastine:

#### ***Hepatic Impairment***

No significant difference was found in  $t_{1/2}$ ,  $C_{max}$  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 **PRECAUTIONS – Use in Patients with Hepatic Impairment**).

#### ***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 **PRECAUTIONS – Use in Patients with Renal Impairment**).

#### ***Age***

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.

The efficacy and safety of DYLASTINE 125/50 in children under 12 years of age have not been established (see **PRECAUTIONS – Use in Children and Adolescents**).

#### ***Race***

The effect of race has not been evaluated.

## **CLINICAL TRIALS**

The efficacy of DYLASTINE 125/50 was established in four randomised, double-blind, placebo-controlled studies in subjects with seasonal allergic rhinitis (SAR), namely MP4001, MP4002, MP4004, and MP4006.

Study MP4001 compared DYLASTINE 125/50 with commercial azelastine nasal spray (Astelin<sup>®</sup> 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 DYLASTINE 125/50 with the single compounds in the DYLASTINE 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 1 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, DYLASTINE 125/50 was significantly superior to placebo and the monotherapy components. In addition, each individual component was significantly superior to placebo.

**Table 1: 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	DYLASTINE 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. DYLASTINE 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. DYLASTINE 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. DYLASTINE 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. DYLASTINE 125/50	-	0.029	0.016	< 0.001

\* MP4001: Fluticasone Propionate Nasal Spray from Roxane Laboratories Inc.; Other studies: FLU in DYLASTINE 125/50 vehicle

\*\* MP4001: Astelin<sup>®</sup> Nasal Spray; Other studies: AZE in DYLASTINE 125/50 vehicle

^ DYLASTINE 125/50 vehicle

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

In the meta-analysis that pooled data from the 4 efficacy studies, DYLASTINE 125/50 was shown to be statistically significantly superior to both azelastine and fluticasone monoproductions 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 DYLASTINE 125/50 with azelastine for eye redness ( $p = 0.0513$ ). DYLASTINE 125/50 at least doubled the effect of azelastine and fluticasone propionate in reducing nasal and ocular symptoms score.

The RQLQ score for DYLASTINE 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 DYLASTINE 125/50 and placebo exceeded the minimum clinically significant difference of -0.50.

DYLASTINE 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 DYLASTINE 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.

## **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.

## **CONTRAINDICATIONS**

Hypersensitivity to the active substance(s) or to any of the excipients.

## **PRECAUTIONS**

### **Somnolence**

In clinical studies, the occurrence of somnolence has been reported in some patients taking DYLASTINE 125/50 (see **ADVERSE 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 DYLASTINE 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 DYLASTINE 125/50 is used concomitantly with alcohol or other CNS depressants (see **PRECAUTIONS –Effects on Ability to Drive and Operate Machinery and INTERACTIONS WITH OTHER MEDICINES – 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 DYLASTINE 125/50. 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 DYLASTINE 125/50 until healing has occurred.

Local infections of the nasal airways should be appropriately treated but do not constitute a specific contra-indication to treatment with DYLASTINE 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 (eg diabetics).

### **Glaucoma and Cataracts**

Rare instances of glaucoma and increased intra-ocular pressure have been reported following administration of intranasal corticosteroids, as a class effect. 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.

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 DYLASTINE 125/50 if there is any reason to suppose that their adrenal function is impaired.

### **Use of Cytochrome P450 3A4 Inhibitors**

Care should be taken when co-administering known, strong CYP3A4 inhibitors, eg. ritonavir and ketoconazole, as there is potential for increased systemic exposure to fluticasone propionate. (see **INTERACTIONS WITH OTHER MEDICINES** and **Pharmacokinetics – 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 **PRECAUTIONS – Use in Children and Adolescents**).

### **Use in Patients with Renal Impairment**

See **Pharmacokinetics** under **Special Populations – Renal Impairment**.

### **Use in Patients with Hepatic Impairment**

See **Pharmacokinetics** under **Special Populations – Hepatic Impairment**.

### **Effects on Fertility**

No studies on impairment of fertility were conducted with DYLASTINE 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**

### **Category B3**

There is no or insufficient evidence of safety of DYLASTINE 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 DYLASTINE 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 diaplacental transfer of the drug to the fetuses. 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 DYLASTINE 125/50 is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when DYLASTINE 125/50 is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of DYLASTINE 125/50 by nursing mothers, based on data from the individual components, a decision should be made whether to discontinue nursing or to discontinue DYLASTINE 125/50, taking into account the importance of DYLASTINE 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.

### **Use in Children and Adolescents**

Safety and effectiveness of DYLASTINE 125/50 in pediatric patients below the age of 12 years have not been established.

Retardation of growth rate in children may occur with intranasal steroids, particularly at high doses prescribed for prolonged periods of time (see **PRECAUTIONS – Effect on Growth**).

### **Use in the Elderly**

(See **Pharmacokinetics** under Special Populations – Age)

### **Carcinogenicity**

No studies of carcinogenicity were conducted with DYLASTINE 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.

### **Genotoxicity**

No studies of genotoxicity were conducted with DYLASTINE 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.

### **Effects on Laboratory Tests**

No effects are known.

### **Effects on Ability to Drive or Operate Machinery**

Due to the potential occurrence of somnolence (see **PRECAUTIONS – Somnolence**), patients using DYLASTINE 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 DYLASTINE 125/50 until they know how they react to the nasal spray. Caution is required if DYLASTINE 125/50 is used concomitantly with alcohol or other CNS depressants. (see **PRECAUTIONS – Somnolence** and **INTERACTIONS WITH OTHER MEDICINES – Central Nervous System Depressants**).

### **INTERACTIONS WITH OTHER MEDICINES**

No formal drug interaction studies have been performed with DYLASTINE 125/50. The drug interactions of DYLASTINE 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 DYLASTINE 125/50 is used concomitantly with alcohol or other CNS depressants. (see **PRECAUTIONS – Somnolence** and **Effects on Ability to Drive and Operate Machinery**).

#### **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.

#### **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

**Pharmacokinetics – Metabolism and PRECAUTIONS – 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.

**ADVERSE EFFECTS**

In the 4 placebo-controlled studies (MP4001, MP4002, MP4004 and MP4006), 1006 patients were treated with DYLASTINE 125/50, 1012 with placebo, 851 with azelastine (AZE) in DYLASTINE 125/50 vehicle, 846 with fluticasone propionate (FLU) in DYLASTINE 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. Treatment-emergent adverse events reported with an incidence of ≥ 1% in the DYLASTINE 125/50 treated group, in the 4 pivotal studies, are shown in Table 2.

**Table 2: Treatment-emergent adverse events with an incidence of ≥ 1% in the DYLASTINE 125/50 treated group, in the 4 pivotal studies**

	<b>DYLASTINE 125/50</b>	<b>Placebo</b>	<b>AZE<sup>§</sup></b>	<b>FLU<sup>§</sup></b>	<b>AZE<sup>marketed</sup></b>	<b>FLU<sup>marketed</sup></b>
	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
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 DYLASTINE 125/50 vehicle.

Table 3 listed possible adverse reactions for DYLASTINE 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 3: Possible adverse reactions of DYLASTINE 125/50**

<b>Frequency System Organ Class</b>	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very rare</b>
<b><i>Immune system disorders</i></b>					Hypersensitivity including anaphylactic reactions, angioedema, bronchospasm
<b><i>Nervous system disorder</i></b>		Headache, dysgeusia	Unpleasant smell	Nervousness, taste loss	Dizziness, somnolence (drowsiness, sleepiness)
<b><i>Eye disorders</i></b>					Glaucoma, increased intraocular pressure, cataract
<b><i>Respiratory, thoracic and mediastinal disorders</i></b>			Epistaxis, nasal discomfort (stinging, itching), sneezing, nasal dryness, cough, dry throat, throat irritation		Nasal septal perforation, mucosal erosion
<b><i>Gastrointestinal disorders</i></b>				Dry mouth	Nausea
<b><i>Skin and subcutaneous tissue disorders</i></b>					Rash, pruritus, urticaria
<b><i>General disorders and administration site conditions</i></b>					Fatigue (weariness, exhaustion), weakness

## DOSAGE AND ADMINISTRATION

### Dosage

Adults and adolescents (e.g. 12 years and older)

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

Children below 12 years

DYLASTINE 125/50 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.

Elderly

No dose adjustment is required in this population (see **Pharmacokinetics** under **Special Populations – Age** and **PRECAUTIONS – Use in the Elderly**).

Renal and hepatic impairment

No dose adjustment is required in patients with renal impairment or mild to moderate hepatic impairment (see **Pharmacokinetics** under **Special Populations – Renal Impairment** and **PRECAUTIONS – Use in Renal Impairment**).

There are no data in patients with severe hepatic impairment (see **Pharmacokinetics** under **Special Populations – Hepatic Impairment** and **PRECAUTIONS – Use in Hepatic Impairment**).

### Duration of treatment

DYLASTINE 125/50 nasal spray is suitable for long-term use. There is no restriction regarding duration of use.

### Method of Administration

DYLASTINE 125/50 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, DYLASTINE 125/50 nasal spray must be primed by pressing down and releasing the pump 6 times until a fine mist appears. If DYLASTINE 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.

## OVERDOSAGE

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

DYLASTINE 125/50 nasal spray contains both azelastine and fluticasone propionate; therefore, the risks associated with overdosage for the individual components apply to DYLASTINE 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. Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

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.

## **PRESENTATION AND STORAGE CONDITIONS**

### **Presentation**

DYLASTINE 125/50 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. The available pack sizes are:

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

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

### **Storage Conditions**

DYLASTINE 125/50 nasal spray should be kept out of reach of children. Store below 25°C. Do not refrigerate. Do not freeze. Discard after 6 months of first opening the bottle.

**Attachment 1: Product information for AusPAR fluticasone propionate and azelastine hydrochloride Dymista/Dylastine Meda Pharmaceuticals PM-2012-03466-1-5 Final 24 July 2014. This Product Information was approved at the time this AusPAR was published.**

Product Information v3

Meda Pharmaceuticals Pty Ltd

## **POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

### **SPONSOR**

MEDA Pharmaceuticals Pty Ltd  
Suite 1, Level 3, 110 Pacific Highway  
ST LEONARDS NSW 2065  
Australia  
Telephone: 1800 048 987



**Date of TGA Approval:** 16 December 2013.

Australian Registration Number AUST R 203132.



## DYMISTA<sup>®</sup> 125/50

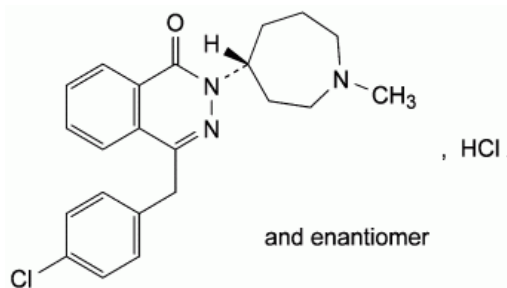
### Nasal Spray

## PRODUCT INFORMATION

### NAME OF THE MEDICINE

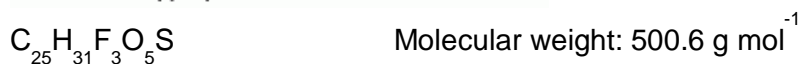
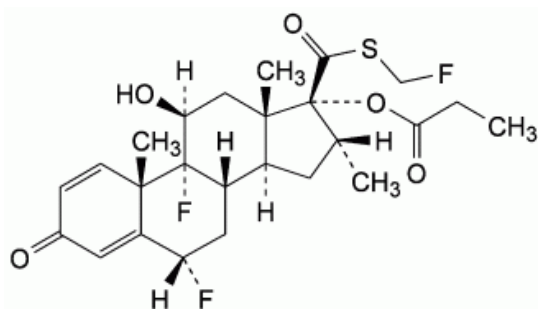
Azelastine hydrochloride and fluticasone propionate

The chemical name for azelastine hydrochloride is (*R,S*)-4[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-phthalazin-1(2*H*)-one hydrochloride. Azelastine hydrochloride has the following chemical structure:



CAS Registry No: 79307-93-0

The chemical name for fluticasone propionate is 6 $\alpha$ ,9-Difluoro-17-[[[(fluoromethyl) sulphanyl]carbonyl]-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-dien-17 $\alpha$ -yl] propanoate. Fluticasone propionate has the following chemical structure:



CAS Registry No: 80474-14-2

## **DESCRIPTION**

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

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.

DYMISTA 125/50 nasal spray contains the following inactive ingredients: disodium edetate, glycerol, microcrystalline cellulose, carmellose sodium, polysorbate 80, benzalkonium chloride, phenethyl alcohol and purified water.

### **Physical and Chemical Properties**

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

## **PHARMACOLOGY**

### **Pharmacodynamics**

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 H<sub>1</sub>-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 H<sub>1</sub> – 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.

### **Pharmacokinetics**

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<sub>max</sub>) 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<sub>max</sub>) 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 **PRECAUTIONS – Use of Cytochrome P450 3A4 Inhibitors**) and **INTERACTIONS WITH OTHER MEDICINES**).

### **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 125/50 was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained. The following data are available for the individual active component, azelastine:

#### ***Hepatic Impairment***

No significant difference was found in  $t_{1/2}$ ,  $C_{max}$  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 **PRECAUTIONS – Use in Patients with Hepatic Impairment**).

#### ***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 **PRECAUTIONS – Use in Patients with Renal Impairment**).

#### ***Age***

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.

The efficacy and safety of DYMISTA 125/50 in children under 12 years of age have not been established (see **PRECAUTIONS – Use in Children and Adolescents**).

#### ***Race***

The effect of race has not been evaluated.

## **CLINICAL TRIALS**

The efficacy of DYMISTA 125/50 was established in four randomised, double-blind, placebo-controlled studies in subjects with seasonal allergic rhinitis (SAR), namely MP4001, MP4002, MP4004, and MP4006.

Study MP4001 compared DYMISTA 125/50 with commercial azelastine nasal spray (Astellin<sup>®</sup> 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 1 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.

**Attachment 1: Product information for AusPAR fluticasone propionate and azelastine hydrochloride Dymista/Dylastine Meda Pharmaceuticals PM-2012-03466-1-5 Final 24 July 2014. This Product Information was approved at the time this AusPAR was published.**

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**Table 1: 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<sup>®</sup> 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.

## **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.

## **CONTRAINDICATIONS**

Hypersensitivity to the active substance(s) or to any of the excipients.

## **PRECAUTIONS**

### **Somnolence**

In clinical studies, the occurrence of somnolence has been reported in some patients taking DYMISTA 125/50 (see **ADVERSE 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 **PRECAUTIONS –Effects on Ability to Drive and Operate Machinery and INTERACTIONS WITH OTHER MEDICINES – 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, nasal surgery, or nasal trauma 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 contra-indication 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 (eg diabetics).

### **Glaucoma and Cataracts**

Rare instances of glaucoma and increased intra-ocular pressure have been reported following administration of intranasal corticosteroids, as a class effect. 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.

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.

### **Use of Cytochrome P450 3A4 Inhibitors**

Care should be taken when co-administering known, strong CYP3A4 inhibitors, eg. ritonavir and ketoconazole, as there is potential for increased systemic exposure to fluticasone propionate. (see **INTERACTIONS WITH OTHER MEDICINES** and **Pharmacokinetics – 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 **PRECAUTIONS – Use in Children and Adolescents**).

### **Use in Patients with Renal Impairment**

See **Pharmacokinetics** under **Special Populations – Renal Impairment**.

### **Use in Patients with Hepatic Impairment**

See **Pharmacokinetics** under **Special Populations – Hepatic Impairment**.

### **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**

### **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 diaplacental transfer of the drug to the fetuses. 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 embryoletality 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.

### **Use in Children and Adolescents**

Safety and effectiveness of DYMISTA 125/50 in pediatric patients below the age of 12 years have not been established.

Retardation of growth rate in children may occur with intranasal steroids, particularly at high doses prescribed for prolonged periods of time (see **PRECAUTIONS – Effect on Growth**).

### **Use in the Elderly**

(See **Pharmacokinetics** under Special Populations – Age)

### **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.

### **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.

### **Effects on Laboratory Tests**

No effects are known.

### **Effects on Ability to Drive or Operate Machinery**

Due to the potential occurrence of somnolence (see **PRECAUTIONS – 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 **PRECAUTIONS – Somnolence** and **INTERACTIONS WITH OTHER MEDICINES – Central Nervous System Depressants**).

## **INTERACTIONS WITH OTHER MEDICINES**

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 **PRECAUTIONS – Somnolence** and **Effects on Ability to Drive and Operate Machinery**).

### **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.

#### **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 **Pharmacokinetics – Metabolism** and **PRECAUTIONS – 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.

## ADVERSE EFFECTS

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<sup>®</sup> 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. Treatment-emergent adverse events reported with an incidence of  $\geq 1\%$  in the DYMISTA 125/50 treated group, in the 4 pivotal studies, are shown in Table 2.

**Table 2: Treatment-emergent adverse events with an incidence of  $\geq 1\%$  in the DYMISTA 125/50 treated group, in the 4 pivotal studies**

	<b>DYMISTA 125/50</b>	<b>Placebo</b>	<b>AZE<sup>§</sup></b>	<b>FLU<sup>§</sup></b>	<b>AZE<sup>marketed</sup></b>	<b>FLU<sup>marketed</sup></b>
	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
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 3 listed possible adverse reactions for DYMISTA 125/50, with frequencies corresponding to:

- Very common ( $\geq 1/10$ )
- Common ( $\geq 1/100$  to  $< 1/10$ )
- Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )
- Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )
- Very rare ( $< 1/10,000$ )
- Not known (cannot be estimated from the available data)

**Table 3: Possible adverse reactions of DYMISTA 125/50**

Frequency System Organ Class	Very common	Common	Uncommon	Rare	Very rare
<i>Immune system disorders</i>					Hypersensitivity including anaphylactic reactions, angioedema, bronchospasm
<i>Nervous system disorder</i>		Headache, dysgeusia	Unpleasant smell	Nervousness, taste loss	Dizziness, somnolence (drowsiness, sleepiness)
<i>Eye disorders</i>					Glaucoma, increased intraocular pressure, cataract
<i>Respiratory, thoracic and mediastinal disorders</i>			Epistaxis, nasal discomfort (stinging, itching), sneezing, nasal dryness, cough, dry throat, throat irritation		Nasal septal perforation, mucosal erosion
<i>Gastrointestinal disorders</i>				Dry mouth	Nausea
<i>Skin and subcutaneous tissue disorders</i>					Rash, pruritus, urticaria
<i>General disorders and administration site conditions</i>					Fatigue (weariness, exhaustion), weakness

## DOSAGE AND ADMINISTRATION

### Dosage

Adults and adolescents (e.g. 12 years and older)

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

#### Children below 12 years

DYMISTA 125/50 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.

#### Elderly

No dose adjustment is required in this population (see **Pharmacokinetics** under **Special Populations – Age** and **PRECAUTIONS – Use in the Elderly**).

#### Renal and hepatic impairment

No dose adjustment is required in patients with renal impairment or mild to moderate hepatic impairment (see **Pharmacokinetics** under **Special Populations – Renal Impairment** and **PRECAUTIONS – Use in Renal Impairment**).

There are no data in patients with severe hepatic impairment (see **Pharmacokinetics** under **Special Populations – Hepatic Impairment** and **PRECAUTIONS – Use in Hepatic Impairment**).

#### **Duration of treatment**

DYMISTA 125/50 nasal spray is suitable for long-term use. There is no restriction regarding duration of use.

#### **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. 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.

#### **OVERDOSAGE**

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.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

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.

## **PRESENTATION AND STORAGE CONDITIONS**

### **Presentation**

DYMISTA 125/50 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. The available pack sizes are:

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

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

### **Storage Conditions**

DYMISTA 125/50 nasal spray should be kept out of reach of children. Store below 25°C. Do not refrigerate. Do not freeze. Discard after 6 months of first opening the bottle.

## **POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

**Attachment 1: Product information for AusPAR fluticasone propionate and azelastine hydrochloride Dymista/Dylastine Meda Pharmaceuticals PM-2012-03466-1-5 Final 24 July 2014. This Product Information was approved at the time this AusPAR was published.**

Product Information v3

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