SCHEDULING STATUS: S2

1 NAME OF THE MEDICINE

DYMISTA® NASAL SPRAY

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g of suspension contains 1 mg azelastine hydrochloride and 0,365 mg fluticasone propionate.

Each actuation (0,14 g) delivers 137 micrograms azelastine hydrochloride (= 125 micrograms azelastine) and 50 micrograms fluticasone propionate.

Preservatives: Benzalkonium chloride 0,01 % m/m (0,014 mg per actuation) and phenylethyl alcohol 0,25 % m/m (0,343 mg per actuation).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, suspension

White, homogeneous, redispersible suspension free from visible foreign matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DYMISTA NASAL SPRAY is indicated for the treatment of seasonal and perennial allergic rhinitis (including hay fever) and rhino-conjunctivitis in adults if the use of either intranasal antihistamine or corticosteroid alone is not sufficient.

DYMISTA NASAL SPRAY is also indicated for short term treatment of seasonal allergic rhinitis in children above the age of 12 years if the use of either intranasal antihistamine or corticosteroid alone is not sufficient.

4.2 Posology and method of administration

Posology

For full therapeutic benefit regular usage is essential.

Contact with the eyes should be avoided.

Adults and children (over 12 years of age)

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

Paediatric population

Children 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.

Special populations

Elderly population

No dose adjustment is required in this population.

Renal and hepatic impairment

There are no data in patients with renal and hepatic impairment.

Duration of treatment

DYMISTA NASAL SPRAY is suitable for long-term use.

The duration of treatment should correspond to the period of allergenic exposure.

Method of administration

DYMISTA NASAL SPRAY is for nasal use only.

Instruction for use

Preparing the spray

The bottle should be shaken gently before use for about 5 seconds by tilting it upwards and downwards and the protective cap be removed afterwards. Prior to first use DYMISTA NASAL SPRAY must be primed by pressing down and releasing the pump 6 times. If DYMISTA NASAL SPRAY has not been used for more than 7 days it must be reprimed once by pressing down and releasing the pump.

Using the spray

After blowing the nose the suspension is to be sprayed once into each nostril keeping the head tilted downward (see figure). After use, the spray tip is to be wiped and the protective cap to be replaced.



4.3 Contraindications

Known hypersensitivity to azelastine hydrochloride, fluticasone propionate, or any of the excipients of DYMISTA NASAL SPRAY (listed in section 6.1).

4.4 Special warnings and precautions for use

Somnolence

Somnolence has been reported in some patients using DYMISTA NASAL SPRAY in trials (see section 4.8). Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as operating machinery or driving a motor vehicle after administration of DYMISTA NASAL SPRAY. Concurrent use of DYMISTA NASAL SPRAY with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur (see section 4.5 and 4.7).

Local nasal effects

In clinical trials, epistaxis was observed more frequently in patients treated with DYMISTA NASAL SPRAY than those who received placebo (see section 4.8).

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 trials with DYMISTA NASAL SPRAY.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should avoid use of DYMISTA NASAL SPRAY until healing has occurred.

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

Glaucoma and cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Glaucoma and cataract formation were evaluated with intraocular pressure measurements and slit lamp examinations in a clinical study in adolescent and adult patients aged 12 years and older with perennial allergic or vasomotor rhinitis (VMR). In the DYMISTA NASAL SPRAY group, one patient had increased intraocular pressure at month 6. In addition, three patients had evidence of posterior subcapsular cataract at month 6 and one at month 12 (end of treatment). In the fluticasone propionate group, three patients had evidence of posterior subcapsular cataract at month 12 (end of treatment).

Immunosuppression

Persons who are using medicines, such as corticosteroids, that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex because of the potential for worsening of these

infections.

Hypothalamic-pituitary-adrenal (HPA) axis effects

When intranasal steroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercortisolism and adrenal suppression may appear. If such changes occur, the dosage of DYMISTA NASAL SPRAY should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy. The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercortisolism and/or suppression of the HPA axis.

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal e.g. joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Use of cytochrome P450 3A4 inhibitors

Ritonavir and other strong cytochrome P450 3A4 (CYP3A4) inhibitors can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see sections 4.5 and 5.2). During post-marketing use, there have been reports of clinically significant medicine interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of DYMISTA NASAL SPRAY and ritonavir is not recommended.

Use caution with the coadministration of DYMISTA NASAL SPRAY and other potent CYP3A4 inhibitors, such as ketoconazole (see sections 4.5 and 5.2).

Effect on growth

Corticosteroids may cause growth retardation when administered to paediatric patients. Growth should be routinely monitored in paediatric patients receiving DYMISTA NASAL SPRAY (see section 4.8).

DYMISTA NASAL SPRAY contains benzalkonium chloride. Benzalkonium chloride may cause irritation or swelling of the nasal mucosa and bronchospasm especially if used for a long time.

4.5 Interaction with other medicines and other forms of interaction

Fluticasone propionate

Under normal circumstances, 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.

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

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.

Azelastine hydrochloride

No specific interaction studies with azelastine hydrochloride nasal spray have been performed. Interaction studies at high oral doses have been performed. However, they bear no relevance to azelastine nasal spray as given recommended nasal doses result in much lower systemic exposure. Nevertheless, care should be taken when administering azelastine hydrochloride in patients taking concurrent sedative or central nervous medications because sedative effect may be enhanced. Alcohol may also enhance this effect (see section 4.7).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of azelastine hydrochloride and fluticasone propionate in pregnant women.

There are no adequate and well-controlled clinical trials of DYMISTA NASAL SPRAY, azelastine hydrochloride only, or fluticasone propionate only in pregnant women. Animal reproductive studies of azelastine hydrochloride and fluticasone propionate in mice, rats, and/or rabbits revealed evidence of teratogenicity as well as other developmental toxic effects.

Azelastine hydrochloride

Azelastine hydrochloride has shown teratogenic effects in experimental animals, such as mice, rats and rabbits.

Effects such as embryo-foetal death, malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification, and decreased foetal weight and maternal toxicity occurred in mice.

In rats, azelastine hydrochloride caused malformations (oligo- and brachydactylia), delayed ossification and skeletal variations, in the absence of maternal toxicity. Azelastine hydrochloride also caused embryo-foetal death and decreased foetal weight at higher doses. This also caused severe maternal toxicity.

In rabbits, azelastine hydrochloride caused abortion, delayed ossification, and decreased foetal weight and also resulted in severe maternal toxicity.

Fluticasone propionate

Fluticasone propionate has also shown teratogenic effects. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

In the rabbit, foetal weight reduction, skeletal variations, omphalocele and cleft palate were observed.

Nonteratogenic effects

Fluticasone propionate crossed the placenta following oral administration of approximately 4 and 25 times the MRHDID (Maximum Recommended Human Daily Inhalation Dose) in adult rats and rabbits.

Breastfeeding

It is not known whether DYMISTA NASAL SPRAY is excreted in human breast milk. Caution should be exercised when DYMISTA NASAL SPRAY is administered to breastfeeding women (see section 5.3).

Fertility

There are only limited data with regard to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

DYMISTA NASAL SPRAY has minor influence on the ability to drive and use machines.

Fatigue, weariness, exhaustion, dizziness, weakness or blurred vision that may also be caused by the disease itself, may occur when using DYMISTA NASAL SPRAY. In these cases, the ability to drive and use machines may be impaired. Alcohol may enhance this effect.

4.8 Undesirable effects

a. Summary of the safety profile

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).

b. Tabulated list of adverse reactions

The following undesirable effects have been observed and reported during treatment with DYMISTA NASAL SPRAY with the following frequencies: 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).

MedDRA system organ class	Frequency	Adverse reactions
Immune system disorders	Very rare	Hypersensitivity including anaphylactic reactions, angioedema (oedema of the face or tongue and skin rash), bronchospasm
Nervous system disorders	Common	Headache, dysgeusia (unpleasant taste), unpleasant smell
	Very rare	Dizziness, somnolence (drowsiness, sleepiness)
Eye disorders	Very rare	Glaucoma, increased intraocular pressure, cataract
	Not known	Blurred vision (see also section 4.4)
Respiratory, thoracic and	Very common	Epistaxis

mediastinal disorders	Uncommon	Nasal discomfort (including nasal irritation, stinging, itching), sneezing, nasal dryness, cough, dry throat, throat irritation
	Very rare	Nasal septal perforation**, mucosal erosion
Gastrointestinal disorders	Rare	Dry mouth
	Very rare	Nausea
Skin and subcutaneous tissue disorders	Very rare	Rash, pruritus, urticaria
General disorders and administration site conditions	Very rare	Fatigue (weariness, exhaustion), weakness (see section 4.7)

* 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.

c. Description of selected adverse reactions

Common adverse reactions include the following:

- Dysgeusia which is a substance-specific unpleasant taste that may be experienced after administration.
- Epistaxis which involves bleeding from the inside of the nose.

d. Paediatric population

Use of DYMISTA NASAL SPRAY in short term trials for seasonal allergic rhinitis have reported dysgeusia and epistaxis in children 6 – 11 years of age (see section 5.1).

Growth retardation has been reported in children receiving nasal corticosteroids. Growth retardation may also be possible in adolescents (see section 4.4).

e. Other special populations

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

Systemic effects of some nasal corticosteroids may occur, particularly when administered at high doses for prolonged periods (see section 4.4).

In rare cases osteoporosis was observed when nasal glucocorticoids were administered long-term.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

There are no data from patients available on the effects of acute or chronic overdosage with intranasal fluticasone propionate.

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

Administration of doses higher than those recommended over a long period of time may lead to temporary suppression of adrenal function.

In these patients, treatment with DYMISTA NASAL SPRAY should be continued at a dose sufficient to control symptoms; the adrenal function will recover in a few days and can be verified by measuring plasma cortisol.

In the event of overdose after incidental oral uptake, disturbances of the central nervous system (including drowsiness, confusion, coma, tachycardia and hypotension) caused by azelastine hydrochloride are to be expected based on the results of animal experiments.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.5.1 Corticosteroids and analogues

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

Mechanism of action and pharmacodynamic effects

DYMISTA NASAL SPRAY contains azelastine hydrochloride and fluticasone propionate, which have different modes of action and show synergistic effects in terms of improvement of allergic rhinitis and rhino-conjunctivitis symptoms.

Fluticasone propionate

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

Azelastine hydrochloride

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

A relief of nasal allergic symptoms is observed within 15 minutes after administration. Azelastine hydrochloride in DYMISTA NASAL SPRAY is administered as a racemic mixture with no difference in pharmacologic activity noted between the enantiomers in *in vitro* studies. The major metabolite, desmethylazelastine, also possesses H1-receptor antagonist activity.

Azelastine nasal spray has 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.

Clinical safety and efficacy

Adults and adolescents 12 years of age and older

The efficacy and safety of DYMISTA NASAL SPRAY was evaluated in four randomised, double-blind, placebo-controlled, pivotal studies in subjects with seasonal allergic rhinitis (SAR). Safety and efficacy of DYMISTA NASAL SPRAY was further assessed in a 12-month study in subjects with chronic allergic or vasomotor rhinitis. One further study was performed to assess the onset of action of DYMISTA NASAL SPRAY using a standardised Environmental Exposure Chamber (EEC) model.

Efficacy results

Short-term studies

Across the individual studies, DYMISTA NASAL SPRAY was significantly superior to placebo and the monotherapy components. In addition, each individual component was significantly superior to placebo. In the meta-analysis of pooled data, DYMISTA NASAL SPRAY 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.

Long-term study

The superior effect of DYMISTA NASAL SPRAY to fluticasone propionate nasal spray was maintained throughout a 12-month study in patients with chronic persistent allergic rhinitis and nonallergic/vasomotor rhinitis.

Chamber study

In the Environmental Exposure Chamber (EEC) study relief of allergic rhinitis symptoms was observed from 5 minutes after first dose of DYMISTA NASAL SPRAY for nasal (TNSS) and 10 minutes for ocular symptoms (TOSS) ($p < 0,05$). The onset of effect was at least two hours earlier than that observed with a free combination of intranasal fluticasone propionate and an oral antihistamine.

Safety results

Short-term studies

The most frequently reported treatment-emergent adverse events (TEAE) were dysgeusia, epistaxis and headache.

Long-term study

The most frequently reported TEAE (≥ 2 %) with DYMISTA NASAL SPRAY were headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhoea, and epistaxis.

Children 6 to 11 years of age

Two clinical trials evaluated efficacy and safety of DYMISTA NASAL SPRAY in children.

Efficacy results

Results of the original analyses were numerically supportive, but did not achieve statistical significance. The post hoc analyses showed greater treatment differences between DYMISTA NASAL SPRAY and placebo with increasing degree of child self-rating. The improvement in daily overall allergy symptom severity score was statistically significant superior in DYMISTA NASAL SPRAY group than in fluticasone group.

Safety results

The most frequently reported TEAEs (≥ 2 %) in the DYMISTA NASAL SPRAY group were dysgeusia, epistaxis, headache, oropharyngeal pain, vomiting, upper abdominal pain, cough, pyrexia, otitis media, upper respiratory tract infection, diarrhoea, nausea, otitis externa, and urticaria.

5.2 Pharmacokinetic properties

Absorption

After intranasal administration of two sprays per nostril (548 mcg of azelastine hydrochloride and 200 mcg of fluticasone) 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 propionate and the mean total exposure (AUC) was 4217 ± 2618 pg/mL*hr for azelastine and 97,7 ± 43,1 pg/mL*hr for fluticasone. The median time to peak exposure (T_{max}) from a single dose was 0,5 hours for azelastine and 1,0 hours for fluticasone.

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

Fluticasone systemic exposure was ~50 % increased comparing DYMISTA NASAL SPRAY with a marketed fluticasone nasal spray. DYMISTA NASAL SPRAY was equivalent to a marketed azelastine nasal spray with respect to azelastine systemic exposure. There was no evidence of pharmacokinetic interactions between azelastine hydrochloride and fluticasone propionate.

Distribution

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

The volume of distribution of azelastine is high indicating distribution predominantly into the peripheral tissue. The level of protein binding is 80 – 90 %. Additionally, both medicines have broad therapeutic windows. Therefore, medicine displacement reactions are unlikely. *In vitro* studies with human plasma indicate that the plasma protein binding of azelastine hydrochloride and its metabolite, desmethylazelastine, are approximately 88 % and 97 %, respectively.

Biotransformation

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. Azelastine is metabolized to N-desmethylazelastine via various CYP isoenzymes, mainly CYP3A4, CYP2D6 and CYP2C19.

Elimination

The elimination rate of intravenous administered fluticasone propionate is linear over the 250 – 1 000 microgram dose range and are 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.

Plasma elimination half-lives after a single dose of azelastine are approximately 20 – 25 hours for azelastine and about 45 hours for the therapeutically active metabolite N-desmethylazelastine. Excretion occurs mainly via the faeces. The sustained excretion of small amounts of the dose in the faeces suggests that some enterohepatic circulation may take place.

5.3 Preclinical safety data

Fluticasone propionate

Findings in general toxicology studies were similar to those observed with other glucocorticoids and are associated with exaggerated pharmacological activity. These findings are not likely to be relevant for humans given recommended nasal doses which results in minimal systemic exposure. No genotoxic effects of fluticasone propionate have been observed in conventional genotoxicity tests. Further, there were no treatment-related increases in the incidence of tumours in two-year inhalation studies in rats and mice.

In animal studies glucocorticoids have been shown to induce malformations including cleft palate and intra-uterine growth retardation. Again this is not likely to be relevant for humans given recommended nasal doses which results in minimal systemic exposure (see section 5.2).

Azelastine hydrochloride

Azelastine hydrochloride displayed no sensitising potential in the guinea pig. Azelastine demonstrated

no genotoxic potential in a battery of *in vitro* and *in vivo* tests, nor any carcinogenic potential in rats or mice. In male and female rats, azelastine at oral doses greater than 3 mg/kg/day caused a dose-related decrease in the fertility index; no substance-related alterations were found in the reproductive organs of males or females during chronic toxicity studies, however, embryotoxic and teratogenic effects in rats, mice and rabbits occurred only at maternal toxic doses (for example, skeletal malformations were observed in rats and mice at doses of 68.6 mg/kg/day).

DYMISTA NASAL SPRAY

Repeated dose intranasal toxicity studies in rats for a period up to 90 days and in dogs for 14 days with DYMISTA NASAL SPRAY revealed no new adverse effects in comparison to the individual components.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Carmellose sodium

Disodium edetate

Glycerol

Microcrystalline cellulose

Phenylethyl alcohol

Polysorbate 80

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 mL pack: 18 months

17 mL pack: 24 months

In-use shelf-life (after first use): 6 months

6.4 Special precautions for storage

Store at or below 30 °C.

Do not refrigerate or freeze.

6.5 Nature and contents of container

The product is presented in the following marketable packs:

DYMISTA NASAL SPRAY is filled into Ph. Eur. Type I 10 mL amber glass bottle or a Ph. Eur. Type I 25 mL amber glass bottle.

Each bottle is fitted with a spray pump and a nasal applicator (actuator) assembled with a dust cap.

The spray pump is crimped to the glass bottle and cannot be taken apart.

Pack sizes of 4 mL or 17 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

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Isando

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Tel.: +27(0)11 451 1300

Manufacturer: Cipla Limited, Pithampur, India

8 REGISTRATION NUMBER

55/21.5.1/0573

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

31 October 2023

10 DATE OF REVISION OF THE TEXT

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ZIMBABWE: P.P.

Reg. No.: (To be allocated)