For the use only of a registered Medicinal Practitioner or a hospital or a Laboratory

RYALTRIS® (Olopatadine and Mometasone Furoate Nasal Spray 600 mcg/25 mcg)

COMPOSITION

Each spray delivers :
Olopatadine hydrochloride USP equivalent to
Olopatadine ….. 600 mcg
Mometasone Furoate Monohydrate Ph.Eur.
equivalent to Mometasone furoate..... 25 mcg
Preservative:
Benzalkonium chloride NF----0.02%w/w

Excipient with known effect:
One actuation delivers 0.02 mg Benzalkonium chloride.

PHARMACEUTICAL FORM

Nasal Spray, Suspension

ACTION AND CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use. ATC code: R01AD59

Mechanism of Action

RYALTRIS® contains both olopatadine hydrochloride and mometasone furoate; therefore, the mechanisms of action described below for the individual components would apply to RYALTRIS® . These drugs represent 2 different classes of medications (histamine H1- receptor antagonist and synthetic corticosteroid).

Olopatadine Hydrochloride
Olopatadine is a histamine H1-receptor antagonist. The antihistaminic activity of olopatadine has been documented in isolated tissues, animal models, and humans.

Mometasone Furoate
Mometasone furoate is a glucocorticosteroid with local anti-inflammatory properties at doses that are minimally systemically active.

Pharmacodynamics

Olopatadine Hydrochloride

Cardiac effects: In a placebo-controlled cardiovascular safety study, 32 healthy volunteer received 20 mg oral solution of olopatadine twice daily for 14 days (8-fold greater daily dose than the recommended daily nasal dose). The mean QTcF (QT corrected for Fridericia's correction method for heart rate) change from baseline was -2.7 msec and -3.8 msec for olopatadine, and placebo, respectively. In this study, 8 subjects treated with olopatadine had a QTcF change from baseline of 30 – 60 msec, 1 subject had a QTcF change from baseline greater than 60 msec, and no subjects had QTcF values greater than 500 msec. Eight subjects treated with placebo had a QTcF change from baseline 30 – 60 msec, no subjects had a QTcF change from baseline greater than 60 msec, and no subjects had QTcF values greater than 500 msec. In a 12-month study in 429 perennial allergic rhinitis patients treated with olopatadine hydrochloride nasal spray, 665 mcg per spray, 2 sprays per nostril twice daily, no evidence of any effect of olopatadine hydrochloride on QT prolongation was observed.

Mometasone Furoate Monohydrate

In two clinical studies utilizing nasal antigen challenge, mometasone furoate monohydrate aqueous nasal spray has shown anti-inflammatory activity in both the early- and late-phase allergic responses. This has been demonstrated by decreases (vs. placebo) in histamine and eosinophil activity and reductions (vs. baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins. The clinical significance of these findings is not known.

Pharmacokinetics Absorption:

After repeated intranasal administration of 2 sprays per nostril of RYALTRIS® (2660 mcg of olopatadine hydrochloride and 100 mcg of mometasone furoate) twice daily in patients with seasonal allergic rhinitis, the mean (± standard deviation) peak plasma exposure (Cmax) was 19.80 ± 7.01 ng/mL for olopatadine and 9.92 ± 3.74 pg/mL for mometasone furoate, and the mean exposure over the dosing regimen (AUCtau) was 88.77 ± 23.87 ng/mL*hr for olopatadine and 58.40 ± 27.00 pg/mL*hr for mometasone furoate. The median time to peak exposure from a single dose was 1 hour for both olopatadine and mometasone furoate.

The systemic bioavailability of olopatadine and mometasone furoate from RYALTRIS® following intranasal administration was estimated to be comparable with olopatadine hydrochloride and mometasone furoate nasal sprays administered as monotherapies.

Distribution:

The protein binding of olopatadine was moderate at approximately 55% in human serum and independent of drug concentration over the range of 0.1 to 1000 ng/mL. Olopatadine binds predominately to human serum albumin.

The in vitro protein binding for mometasone furoate was reported to be 98% to 99% in concentration range of 5 to 500 ng/mL.

Metabolism:

Olopatadine is not extensively metabolized. Based on plasma metabolite profiles following oral administration of [14C] olopatadine, at least 6 minor metabolites circulate in human plasma. Olopatadine accounts for 77% of peak plasma total radioactivity and all metabolites amounted to <6% combined. Two of these have been identified as the olopatadine N-oxide and N desmethyl olopatadine. In in vitro studies with cDNA- expressed human CYP isoenzymes and flavin-containing monooxygenases (FMO), N- desmethyl olopatadine (Ml) formation was catalyzed mainly by CYP3A4, while olopatadine N-oxide (M3) was primarily catalyzed by FMO1 and

FMO3. Olopatadine at concentrations up to 33900 ng/mL did not inhibit the in vitro metabolism of specific substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The potential for olopatadine and its metabolites to act as inducers of CYP enzymes has not been evaluated.

Studies have shown that any portion of a mometasone furoate dose that is swallowed and absorbed undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Upon in vitro incubation, one of the minor metabolites formed is 6ß-hydroxy-mometasone furoate. In human liver microsomes, the formation of the metabolite is regulated by CYP3A4.

Elimination:
Following single-dose intranasal administration of a combination of olopatadine and mometasone furoate (2660 µg of olopatadine HCl and 200 µg of mometasone furoate), the mean elimination half-lives of olopatadine and mometasone furoate were 8.63 and 18.11 hours, respectively.

Olopatadine is mainly eliminated through urinary excretion. Approximately 70% of a [14C] olopatadine hydrochloride oral dose was recovered in urine with 17% in the feces. Of the drug-related material recovered within the first 24 hours in the urine, 86% was unchanged olopatadine, with the balance comprised of olopatadine N-oxide and N- desmethyl olopatadine.

Any absorbed mometasone furoate is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.

Special Populations and Conditions
Pediatrics: RYALTRIS® pharmacokinetics has not been investigated in patients under 12 years of age (see WARNINGS AND PRECAUTIONS, Special Populations).
Geriatrics: Based on population pharmacokinetic analysis among patients 12 years of age and older, the pharmacokinetics of olopatadine and mometasone furoate with RYALTRIS® was not influenced by age.
Sex: Based on population pharmacokinetic analysis, the pharmacokinetics of olopatadine and mometasone furoate with RYALTRIS® was not influenced by gender.
Ethnic Origin: Based on population pharmacokinetic analysis, the pharmacokinetics of olopatadine and mometasone furoate with RYALTRIS® was not influenced by race.

Hepatic Insufficiency:
No specific pharmacokinetic study examining the effect of hepatic impairment was conducted with RYALTRIS®. Metabolism of olopatadine is a minor route of elimination.
Administration of a single inhaled dose of 400 mcg mometasone furoate to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50 to 105 pcg/mL). The observed peak plasma concentrations appeared to increase with severity of hepatic impairment; however, the numbers of detectable levels were few.
Based on data from the individual components, no adjustment of the dosing regimen of RYALTRIS® is warranted in patients with hepatic impairment.

Renal Insufficiency:
The mean Cmax values for olopatadine following single intranasal doses were not markedly different between healthy subjects (18.1 ng/mL) and patients with mild, moderate, and severe renal impairment (ranging from 15.5 to 21.6 ng/mL). Mean plasma AUC0-12 was 2-fold higher in patients with severe impairment (creatinine clearance <30 mL/min/1.73 m2). In these patients, peak steady-state plasma concentrations of olopatadine were approximately 10-fold lower than those observed after higher, 20 mg oral doses, twice daily, which were well tolerated.
The effects of renal impairment on mometasone furoate pharmacokinetics have not been adequately investigated.

Based on data from the individual components, no adjustment of the dosing regimen of RYALTRIS® is warranted in patients with renal impairment.

CLINICAL PARTICULARS

INDICATIONS

RYALTRIS® (Olopatadine and Mometasone Furoate nasal spray) is indicated for:

- The symptomatic treatment of seasonal or perennial allergic rhinitis and associated ocular symptoms in adults and children of 6 years and older.

DOSAGE AND ADMINISTRATION

Dosing Considerations

A relief of nasal allergic symptoms is observed within 10 minutes after administration of RYALTRIS®. However, since the full effect of RYALTRIS® depends on its regular use, patients must be instructed to take the nasal inhalation at regular intervals.

Recommended Dose and Dosage Adjustment

Adults and Adolescents (12 Years of Age and Older): The recommended dose of RYALTRIS® is two sprays in each nostril twice daily (morning and evening).

Children (6 to 11 Years of Age): The recommended dose of RYALTRIS® is one spray per nostril twice daily (morning and evening).

Administration

Administer RYALTRIS® by the intranasal route only. Avoid spraying RYALTRIS® into the eyes or mouth.
Shake the bottle well before each use.

Priming: Prime RYALTRIS® before initial use by releasing 6 sprays. When RYALTRIS® has not been used for 14 days or more, re-prime by releasing 2 sprays or until a fine mist appears.

Missed Dose

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

CONTRAINDICATIONS

RYALTRIS® is contraindicated for patients who:

- Are hypersensitive to this medicine or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

- Have untreated fungal, bacterial, or tuberculosis infections of the respiratory tract.

WARNINGS AND PRECAUTIONS

General

During transfer from systemic corticosteroid to RYALTRIS®, some patients may experience symptoms of withdrawal from systemically active corticosteroids (e.g., joint and/or muscular pain, lassitude, and depression initially) despite relief from nasal symptoms and will require encouragement to continue RYALTRIS® therapy. Such transfer may also unmask pre-existing allergic conditions such as allergic conjunctivitis and eczema, previously suppressed by systemic corticosteroid therapy.

Driving and Operating Machinery

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Ear/Nose/Throat

In clinical trials of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients treated with RYALTRIS® than those who received placebo [see Clinical Trial Adverse Reactions (7.2)].

RYALTRIS® should not be used in the presence of untreated localized infection involving the nasal mucosa.

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

Instances of nasal ulceration and nasal septal perforation have been reported in patients following the intranasal application of antihistamines. Following the use of intranasal aerosolized corticosteroids, instances of nasal septum perforation have been reported very rarely.

As with any long-term treatment, patients using RYALTRIS® over several months or longer should be examined periodically for possible changes in the nasal mucosa. If localized fungal infection of the nose or pharynx develops, discontinuance of RYALTRIS® therapy or appropriate treatment may be required. Persistence of nasopharyngeal irritation may be an indication for discontinuing RYALTRIS®

Endocrine and Metabolism
Patients who are transferred from long-term administration of systemically active corticosteroids to RYALTRIS® require careful attention. Systemic corticosteroid withdrawal in such patients may result in adrenal insufficiency for a number of months until recovery of hypothalamic-pituitary-adrenal (HPA) axis function. If these patients exhibit signs and symptoms of adrenal insufficiency, systemic corticosteroid administration should be resumed and other modes of therapy and appropriate measures instituted.

Immune
Patients receiving corticosteroids who are potentially immunosuppressed should be warned of the risk of exposure to certain infections (e.g., chickenpox, measles) and of the importance of obtaining medical advice if such exposure occurs.

Ophthalmologic
Following the use of intranasal aerosolized corticosteroids, instances of increased intraocular pressure have been reported very rarely.

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

Sexual Health
Fertility: Studies have not been performed to evaluate the effect of intranasal administration of RYALTRIS® or the respective monotherapies olopatadine hydrochloride and mometasone furoate on human fertility.

Olopatadine administered to male and female rats at oral doses of approximately 810-fold the maximum recommended human daily intranasal dose (MRHDID) (on mg/m2 basis, assuming a human body weight of 60 kg) resulted in a decrease in the fertility index and reduced implantation rate. No effects on fertility were observed at doses of approximately 100-fold the MRHDID on mg/m2 basis.

Mometasone furoate administered subcutaneously to rats at doses of approximately 5- and 1-fold the MRHDID on body weight and mg/m2 basis, respectively did not result in impairment of fertility.

SPECIAL POPULATIONS

Pregnant Women

No adequate and well-controlled studies in pregnant women have been conducted with RYALTRIS® or the respective monotherapies for olopatadine hydrochloride and mometasone furoate.

Olopatadine was not teratogenic in rabbits and rats at oral doses of approximately 1600- and 1200-fold the MRHDID on mg/m2 basis, respectively. However, rats treated at approximately 120-fold or more and rabbits treated at approximately 100-fold or more the MRHDID on mg/m2 basis during the organogenesis showed a decrease in live fetuses (see TOXICOLOGY).

Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Teratology studies were conducted in rats, mice and rabbits by the oral, topical (dermal), and/or subcutaneous routes (see TOXICOLOGY). As with other nasal corticosteroid preparations, mometasone furoate should be used in pregnant women, nursing mothers or women of childbearing age only if the potential benefit justifies the potential risk to the mother, fetus, or infant. Infants born of mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.

Because animal studies are not always predictive of human responses, RYALTRIS® should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Breast-feeding

Olopatadine has been identified in the milk of nursing rats following oral administration.

Glucocorticosteroids are excreted in human milk.

It is unknown whether nasally administered olopatadine hydrochloride/metabolites or mometasone furoate monohydrate/metabolites are excreted in human breast milk. RYALTRIS® should be used by nursing mothers only if the potential benefit to the patient outweighs the potential risks to the infant.

Pediatrics

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Routinely monitor the growth of pediatric patients receiving RYALTRIS® .

The safety and efficacy of RYALTRIS® in children under 6 years of age have not been established. No data are available.

DRUG INTERACTIONS

Overview

No formal drug-drug interaction studies have been performed with RYALTRIS® . Any drug-drug interactions from the combination of olopatadine and mometasone furoate are expected to reflect those of the individual components.

Olopatadine:

In vitro studies have shown that olopatadine does not inhibit metabolic reactions which involve cytochrome P-450 isoenzymes (1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4). Olopatadine is moderately bound to plasma proteins (approximately 55%). These results indicate that olopatadine is unlikely to result in interactions with other concomitantly administered medications.

Mometasone Furoate:
Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites with no major metabolites detected in plasma. Mometasone furoate is metabolized by CYP3A4.

Co-treatment with CYP3A inhibitors, including cobicistat –containing products is expected to increase the risk of systemic corticosteroid 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. Concurrent use of RYALTRIS® 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.

Drug-Drug Interactions
The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 - Established or Potential Drug-Drug Interactions

Proper/Common Name	**Source of Evidence**	**Effect**	**Clinical Comment**
CYP3A inhibitors (*e.g.*,ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nelfinavir, saquinavir, ritonavir, cobicistat-containing products)	Case Study	After oral Administration of ketoconazole, a strong inhibitor of CYP3A4, the mean plasma concentration of orally inhaled mometasone furoate increased, and plasma cortisol levels appeared to decrease.	Co-treatment with CYP3A inhibitors is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

ADVERSE REACTIONS

Adverse Reaction Overview
The most common adverse reactions observed in clinical trials with RYALTRIS® were dysgeusia, headache, epistaxis, and nasal discomfort. No new clinically significant findings were observed as compared with either olopatadine hydrochloride or mometasone furoate alone. The safety profile of RYALTRIS® is typical of that observed with intranasal drugs of the same classes.

Tabulated list of adverse reactions
The following adverse reactions have been reported during clinical studies and post- marketing data and are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) or not known (cannot be estimated from the available data)

Frequency **System Organ Class**	**Common**	**Uncommon**	**Rare**	**Not known**
Infection and infestations			Bacterial vaginosis	
Psychiatric disorders			Anxiety	
			Depression Insomnia	
Nervous system disorder	Dysgeusia (unpleasant taste)	Dizziness Headaches Somnolence	Lethargy Migraine	
Eye disorders			Blurred vision Dry eye Eye discomfort	Cataracts* Glaucoma* Increased intraocular pressure*
Ear and labyrinth disorder			Ear pain	

Respiratory, thoracic and mediastinal disorders	Epistaxis Nasal discomfort	Nasal dryness	Nasal inflammation Nasal mucosal disorder Oropharyngeal pain Sneezing Throat irritation	
Gastrointestinal disorders		Dry mouth Abdominal pain Nausea	Constipation Sore tongue	
General disorders and administration site conditions		Fatigue		
Injury, poisoning and procedural complications			Laceration	

*reported with the use of corticosteroids.

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

Growth retardation has been reported in children receiving nasal corticosteroids. Growth retardation may be possible in adolescents, too (see section 4.5).

Paediatric population

In the paediatric population (children 6 to 11 years of age), at doses half of those in adult populations, the incidence of recorded adverse events in a clinical study in seasonal allergic rhinitis, e.g., dysgeusia (1.3%), headache (1.3%), epistaxis (0.9%) and nasal discomfort (0.9%) was comparable to placebo.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed.

OVERDOSAGE

RYALTRIS® contains both olopatadine hydrochloride and mometasone furoate monohydrate; therefore, the risks associated with overdosage for the individual components described below apply to RYALTRIS®

Olopatadine Hydrochloride:

Symptoms of antihistamine overdose may include drowsiness in adults and, initially, agitation

and restlessness, followed by drowsiness in children. There is no known specific antidote to RYALTRIS® . Should overdose occur, symptomatic or supportive treatment is recommended, taking into account any concomitantly ingested medications.

Mometasone Furoate Monohydrate:
Because the systemic bioavailability is <1% (using a sensitive assay with a lower quantitation limit of 0.25 pg/mL) after administration of mometasone furoate via RYALTRIS® , overdose is unlikely to require any therapy other than observation, followed by initiation of the appropriate prescribed dosage.

NON-CLINICAL TOXICOLOGY

Acute Toxicity

Olopatadine Hydrochloride
The acute toxicity of olopatadine hydrochloride has been investigated in mice, rats and dogs. Mice and rats demonstrated that olopatadine hydrochloride was not an acute toxicity hazard with oral LD50 values greater than 1150 mg/kg and 3870 mg/kg for mice and rats, respectively.

Mometasone Furoate Monohydrate
Two acute inhalation toxicity studies were conducted in mice (i.e., 4-hr whole-body exposure to micronized, pure, mometasone furoate powder). In the first study, the mean estimated doses were 582 mg/kg (in mice) and 394 mg/kg (for rats), assuming 100% deposition. No clinical signs were observed in either species during the 36-day post- exposure observation period. However, lower body weights compared to pre-treatment values were observed in both species. In the second study, rats were exposed by whole body exposure to 0.68 mg/L micronized mometasone furoate powder for 4 hours, and then observed for 3 weeks. Weight loss occurred during the observation period; while rales, ano-genital staining, soft stools and emaciation were the principal clinical observations. At necropsy, several rats had discoloured lungs, small spleens and discoloured brown skin.

Multiple-Dose Toxicity

Olopatadine Hydrochloride and Mometasone Furoate Monohydrate
No test article-related mortality or adverse systemic effects were observed in rats treated intranasally with RYALTRIS® for 13 weeks and no target organs were identified. No evidence of local toxicity was noted. No notable differences were observed between RYALTRIS® and their monotherapy comparators or the placebo. At the no-observed- adverse-effect level (NOAEL) dose (1.064/0.04 mg/day olopatadine HCl/mometasone furoate) in the 13-week rat toxicity study, there is a 2.3- and 8-fold multiple of the MRHDID of monocomponents of RYALTRIS® (5.320 mg olopatadine HCl [4.8 mg olopatadine base] and 0.2 mg mometasone furoate), based on nasal surface area and body surface area, respectively. Based on body weight dose normalization, there is a 48-fold multiple of the MRHDID of 0.089 mg/kg (5.320 mg/day) olopatadine HCl and 0.0033 mg/kg (0.20 mg/day) mometasone furoate, assuming 60 kg body weight. The NOAEL dose of the comparator monocomponent in the study was 1.064 mg/day and 0.04 mg/day for olopatadine HCl and mometasone furoate, respectively.

Olopatadine Hydrochloride
Sub-chronic and chronic oral toxicity studies in rats and dogs demonstrated that the liver and kidney were target organs for olopatadine hydrochloride toxicity. In rats, ophthalmology and hematology parameters were unaffected following chronic administration of olopatadine hydrochloride. In chronic dog studies, ophthalmology, hematology, blood chemistry and organ weight parameters were unaffected by olopatadine hydrochloride administration. The no toxic effect doses were 6 and 5 mg/kg/day in 13- and 52-week repeat dose oral toxicity study in rat and

dogs, respectively.

Mometasone Furoate Monohydrate
The intranasal irritation potential of mometasone furoate aqueous nasal suspensions were assessed in beagle dogs administered daily doses of up to 4.0 mg/dog for three days, one week or one month. The aqueous nasal suspensions did not induce irritation in the nasal mucosa, and no compound-related changes were observed after one month of administration.

Mometasone furoate aqueous nasal suspension was well tolerated in toxicity studies conducted in rats and dogs for 6 months. Rats received doses of up to 0.600 mg/kg or 0.18 mg/day (approximately 182- and 30-fold the MRHDID of 0.2 mg/day mometasone furoate delivered by RYALTRIS® on body weight and mg/m2 basis, respectively; dogs received doses of up to 0.15 mg/kg or 2.0 mg/day (approximately 45- and 24-fold the MRHDID on body weight and mg/m2 basis, respectively). Rats treated with 0.6 mg/kg experienced hair loss on the back during the last 5 weeks, which correlated with hypotrichosis. The no- effect dose for pharmacologic effects in rats was 0.050 mg/kg (approximately 15- and 2- fold the MRHDID on body weight and mg/m2 basis, respectively) based on low body weight gains at higher doses. Dogs treated with 0.15 mg/kg demonstrated eosinophil counts, which were lower than pre-test and concurrent controls after 4, 13 and 26 weeks. In addition, adrenocorticotropic hormone (ACTH) response in the 0.045 and 0.15 mg/kg dose groups was lower than control. These differences were dose-related and were attributed to mometasone furoate. No evidence of nasal irritation was present at any dose in either the rat or the dog study. No target organs of systemic toxicity were identified in either study.

Mometasone furoate aqueous nasal spray was well tolerated when administered intranasally to dogs for one year at doses of up to 2.0 mg/day. In the 2.0 mg/day dose group, an increased incidence of alopecia, minimal decreases in lymphocytes and eosinophils, decreases in basal and post-ACTH cortisol response, lower adrenal gland weights, small or atrophied adrenal glands, epidermal atrophy, minimal splenic lymphoid atrophy, minimal focal epithelial attenuation in the nasal turbinates and retained luminal mucus were observed. Dogs treated with ≥0.2 mg/day demonstrated a dose-related increase in smaller or absent lymphoid aggregates. With the exception of minimally increased retained luminal mucus in the 2.0 mg/day dose group, there was no evidence of irritation or inflammation in the nasal turbinates of mometasone furoate-treated dogs. Thus, the changes in the lymphoid aggregates were considered a localized corticosteroid response associated with application and were not considered to be of toxicologic significance.

Mutagenicity
Olopatadine Hydrochloride
Olopatadine was tested in a series of in vitro and in vivo mutagenesis studies. The results of these studies demonstrated that treatment with olopatadine did not induce genetic mutations or chromosomal aberrations.

Mometasone Furoate Monohydrate

Mometasone furoate was non-mutagenic in the mouse lymphoma assay and the salmonella/mammalian microsome mutagenicity bioassay. Mometasone furoate was negative in the mouse bone marrow erythrocyte micronucleus assay, the rat bone marrow clastogenicity assay, the UDS assay in rat hepatocytes and the mouse mitotic male germ- cell clastogenicity assay, and the Chinese hamster lung cell chromosomal aberrations assay. At cytotoxic doses in Chinese hamster ovary cell cultures, mometasone furoate induced a dose-related increase in simple chromosome aberrations when continuously exposed (7.5 hours) in the non-activation phase, but not in the presence of rat liver S9 fraction. This finding is not considered to be of significance in the risk assessment of mometasone furoate, since the S9 phase of the chromosomal-aberration assay and all in vivo assays were negative.

Carcinogenicity

Olopatadine Hydrochloride

Olopatadine demonstrated no tumorogenic potential in mice at oral doses up to 500 mg/kg/day (approximately 500-fold the MRHDID on mg/m2 basis) for 78 weeks or in rats at oral doses up to 200 mg/kg/day (approximately 500-fold the MRHDID on a mg/m2 basis) for 104 weeks.

Mometasone Furoate Monohydrate

The carcinogenicity potential of inhaled mometasone furoate (aerosol with CFC propellant and surfactant) at concentrations of 0.25 to 2.0 mcg/L was investigated in 24-month studies in mice and rats. Typical glucocorticoid-related effects, including several non-neoplastic lesions, were observed. No statistically significant dose-response relationship was detected for any of the tumour types. The apparent increase in mouse bladder/seminal vesicle mesenchymal tumours is considered to have no relevance in human carcinogenic risk assessment since it is a species- and strain-specific finding with no human correlate. The greater incidence of pancreatic islet cell hyperplasia in male rats who received 1.0 and 2.0 mcg/L is attributed to the well-established metabolic effects (increased glucose and/or insulin resistance) following prolonged administration of glucocorticoids. Increases in pancreatic islet cell tumours, which are induced by other steroids, reflects a non-genotoxic mechanism operative in an endocrinologically uniquely sensitively species.

Reproductive Toxicology

Olopatadine Hydrochloride

In reproductive studies in rats, impairment of fertility (i.e., decreased fertility index, reduced implantation rate) was observed at an oral dose of 400 mg/kg/day (approximately 810-fold the MRHDID on a mg/m2 basis). No effect on fertility was observed at an oral dose of 50 mg/kg/day (approximately 100-fold the MRHDID on a mg/m2 basis).

In an oral embryofetal development study, pregnant rats were dosed throughout the period of organogenesis at doses up to 600 mg/kg/day. A decrease in the number of live fetuses was observed at doses greater or equal to 60 mg/kg/day (approximately 120-fold the MRHDID on a mg/m2 basis). Olopatadine was not teratogenic at any doses up to 600 mg/kg/day (approximately 1200-fold the MRHDID on a mg/m2 basis). In an oral embryofetal development study, pregnant rabbits were dosed throughout the period of organogenesis at doses up to 400 mg/kg/day. A decrease in the number of live fetuses was observed at doses equal to or greater than 25 mg/kg/day (approximately 100-fold the MRHDID on a mg/m2 basis). Olopatadine was not teratogenic at any dose up to 400 mg/kg/day (approximately 1600-fold the MRHDID on a mg/m2 basis).

Further, rats treated with 600 mg/kg/day (approximately 1200-fold the MRHDID on a mg/m2 basis) of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight.

Mometasone Furoate Monohydrate
In subcutaneous Segment I and III studies in rats, mometasone furoate was well tolerated at doses up to 7.5 mcg/kg (approximately 2.3- and 0.4-fold the MRHDID on body weight and mg/m2 basis, respectively). At 15 mcg/kg (approximately 5- and 1-fold the MRHDID on body weight and mg/m2 basis, respectively), prolonged gestation and prolonged and difficult labour occurred with a reduction in offspring survival and body weight gain or body weight gain. There was no effect on fertility. Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Teratology studies were conducted in rats, mice and rabbits by the oral, topical (dermal), and/or subcutaneous routes. Umbilical hernia occurred in rats administered ≥ 600 mcg/kg dermally (approximately 182- and 30-fold the MRHDID on body weight and mg/m2 basis, respectively), cleft palate in mice administered 180 mcg/kg subcutaneously (approximately 55- and 4-fold the MRHDID on body weight and mg/m2 basis, respectively), and gallbladder agenesis, umbilical hernia, and flexed front paws in rabbits administered ≥ 150 mcg/kg dermally (approximately 45- and 15-fold the MRHDID on body weight and mg/m2 basis, respectively). In these teratogenicity studies, there were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice.

PHARMACEUTICAL PARTICULARS
List of excipients:
Microcrystalline cellulose and Carboxymethyl cellulose sodium Dibasic
sodium phosphate heptahydrate
Carboxymethyl cellulose sodium
Benzalkonium Chloride
Sodium chloride Edetate
disodium Polysorbate 80
Hydrochloric acid
Sodium hydroxide Water
for injection

INCOMPATIBILITIES
Not applicable

SHELF LIFE
24 months

SPECIAL PRECAUTIONS FOR STORAGE
Store upright with dust cap below 30°C.Do not refrigerate or freeze.

NATURE AND CONTENTS OF CONTAINER
For 240 Metered Sprays
30ml HDPE bottle crimp-sealed with a nasal spray pump and fitted with an actuator and overcap.

For 120 Metered Sprays:
20ml HDPE bottle crimp-sealed with a nasal spray pump and fitted with an actuator and overcap..

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For 56 Metered Sprays:
20ml HDPE bottle crimp-sealed with a nasal spray pump and fitted with an actuator and overcap.

SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals (Malaysia) Sdn Bhd (660397-W)
D-31-02, Menara Suezcap 1,No. 2, Jalan Kerinchi 59200 Kuala Lumpur Malaysia.

DATE OF REVISION OF THE TEXT

November ,2023

Package leaflet: Information for the patient

RYALTRIS®

Olopatadine and Mometasone Furoate Nasal Spray 600mcg/25mcg

Read this carefully before you start taking **RYALTRIS®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RYALTRIS®** .

What is RYALTRIS® used for?

RYALTRIS® is a prescription medicine used to treat symptoms of seasonal allergic rhinitis (also called "hay fever" caused by allergies to grass, pollen, ragweed, etc.) and perennial allergic rhinitis (year round allergies caused by dust mites, animal dander and molds) and related eye symptoms in patients 6 years of age and older.

How does RYALTRIS® work?

RYALTRIS® helps reduce the symptoms of seasonal and perennial allergic rhinitis (inflammation of the lining of the nose), such as stuffy nose, runny nose, nasal itching, sneezing, eye redness, itchy and watery eyes.

What are the ingredients in RYALTRIS® ?

Medicinal ingredients:	**Olopatadine Hydrochloride** **Mometasone Furoate Monohydrate**
Non-medicinal ingredients:	Benzalkonium chloride, carboxymethyl cellulose sodium, Edetate disodium, Hydrochloric acid, Microcrystalline cellulose and carboxymethyl cellulose sodium, Polysorbate 80, Sodium chloride, sodium hydroxide, Dibasic Sodium Phosphate Heptahydrate and water for injection.

RYALTRIS® comes in the following dosage forms:

Suspension for metered spray: 600 micrograms of olopatadine and 25 micrograms of mometasone furoate per spray

Do not use RYALTRIS® if:

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RYALTRIS® . Talk about any health conditions or problems you may have, including if you:

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

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

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

Other warnings you should know about:
- RYALTRIS® can cause sleepiness or drowsiness. Do not drive, operate machinery, or do anything that needs you to be alert until you know how RYALTRIS® affects you.
- Do not drink alcohol or take any other medicines that may cause you to feel sleepy while using RYALTRIS® .

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RYALTRIS® :
- Ketoconazole (for fungal infections)
- Ritonavir, cobicistat-containing products, atazanavir, indinavir, nelfinavir, or saquinavir (commonly used to treat HIV infection or AIDS)
- Clarithromycin (for bacterial infections)
- Itraconazole (for fungal infections)
- Nefazodone (antidepressant)
- Telithromycin (for pneumonia, an infection of the lungs)

How to take RYALTRIS® :
RYALTRIS™ is for use in your nose only. Do not spray it into your eyes or mouth. UseRYALTRIS® exactly as recommended by your healthcare provider.

RYALTRIS™ relieves the symptoms within 10 minutes. However, you will get the best results if you keep usingRYALTRIS® at regular intervals.

Usual dose:
Adults and Adolescents (12 years of age and older): 2 sprays in each nostril twice a day (morning and evening).

Children (6 to 11 years of age): 1 spray in each nostril twice a day (morning and evening).

Preparing the nasal spray bottle
Before you useRYALTRIS® for the first time, you will need to shake the bottle well and prime the pump.

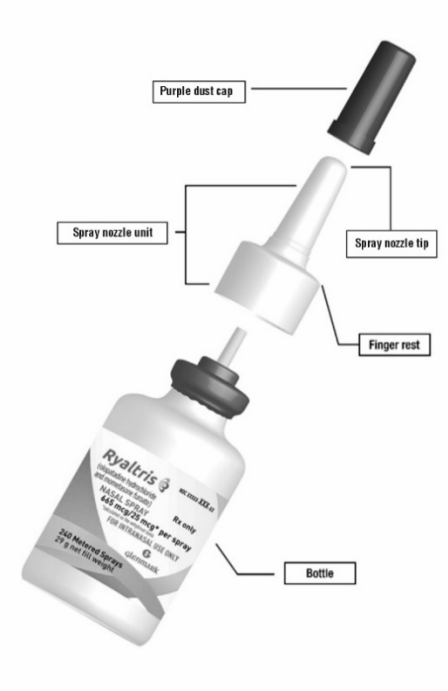
Priming yourRYALTRIS® pump before first use
Before you prime the bottle, shake the bottle well.

Shake container well before each use. The bottle should be discarded after the labelled number of actuations

Diagram of RYALTRIS® nasal spray bottle (See Figure A)

Note: The figures below are intended for illustrative purposes only. Thus, the product labels may not be representative of the actual drug product.

Figure A



Preparing the nasal spray bottle
Before you prime the bottle, shake the bottle for minimum 10 seconds.
Before first use, spray the product 6 times or until a fine mist appears; away from eyes and face.
Step 1. Remove the purple dust cap from the nozzle tip of the bottle. **(See Figure B)**

Figure B

Preparing the nasal spray bottle

Step 2. Hold the nasal spray bottle firmly and upright with your index and middle finger on either side of the spray nozzle unit (on finger rests) while supporting the grooved base of the bottle with your thumb.

- **Step 3.** Before first use, push down on the pump quickly and firmly 6 times, releasing the spray into the air, away from the eyes and face until a fine mist appears. **(See Figure C)**

Figure C

If you do not use RYALTRIS® for 14 or more days, you will need to shake the bottle well, and prime the pump with 2 sprays or until a fine mist appears.

Your RYALTRIS® is now ready for use.

Using your RYALTRIS®

Step 4. Gently blow your nose to clear your nostrils. **(See Figure D)**

Figure D

Step 5. Shake the bottle well before each use (morning and evening).
Step 6. Hold the bottle firmly with your index and middle finger on either side of the spray nozzle unit (on finger rests) while supporting the grooved base of the bottle with your thumb. **(See Figure E)**

Figure E

Step 7. Hold 1 nostril closed with a finger. Insert the end of the spray nozzle tip into the other nostril, pointing it slightly toward the outside of the nose, away from the nasal septum (the wall between the nostrils). **(See Figure F)**

Figure F

Step 8. Tilt your head forward slightly. Keep the bottle upright and press down one time quickly and firmly on the finger rests to activate the pump. **(See Figure G)** Breathe in (inhale) gently through your nose as you spray. Then breathe out through your mouth.

Figure G

Try not to get any spray into your eyes or directly on your nasal septum (the wall between the 2 nostrils).

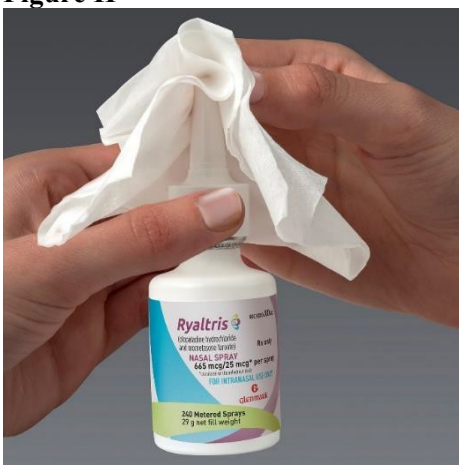
Step 9. Repeat Steps 6 to 8 and deliver a second spray in the same nostril.

Step 10. Repeat Steps 6 to 8 with 2 sprays in the other nostril.

- Do not blow your nose for at least 15 minutes after using RYALTRIS® to make sure that you receive all of the medicine.
- Do not tip your head back. This will keep the medicine from going into your throat.

Step 11. TO PREVENT ANY BLOCKAGE, AFTER EACH USE
Wipe the white spray nozzle tip with a clean dry tissue or cloth. **(See Figure H**Error! Reference source not found.**)**

Figure H



Step 12. HOLD THE NOZZLE UNIT AND PUSH THE PURPLE DUST CAP BACK ON THE NOZZLE UNTIL YOU HEAR A CLICK. (See Figure I)

Figure I

For 240 MD:
Each bottle of RYALTRIS® contains enough medicine for you to spray from the bottle 240 times after the first (initial) priming. You should keep track of the number of sprays used from each bottle of RYALTRIS®. Do not count any sprays used for initial priming of the bottle.

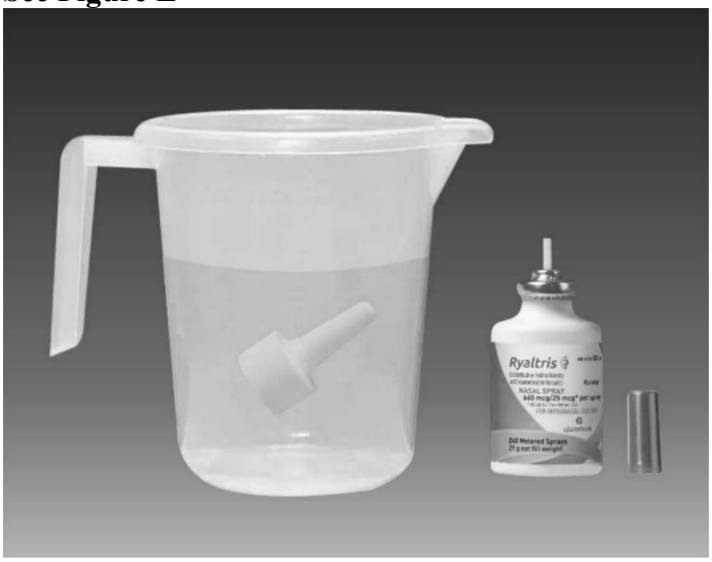
For 120 MD:
Each bottle of RYALTRIS® contains enough medicine for you to spray from the bottle 120 times after the first (initial) priming. You should keep track of the number of sprays used from each bottle of RYALTRIS®.Do not count any sprays used for initial priming of the bottle.

For 56 MD:
Each bottle of RYALTRIS® contains enough medicine for you to spray from the bottle 56 times after the first (initial) priming. You should keep track of the number of sprays used from each bottle of RYALTRIS®. Do not count any sprays used for initial priming of the bottle. Do not count any sprays used for initial priming of the bottle.

How to clear the RYALTRIS® spray pump unit if it becomes clogged:
Do not try to unblock the spray nozzle tip by inserting a pin or other sharp object. (See Figure J) This will damage the spray nozzle tip, and you may not get the correct dose of medicine.
Figure J

Step 13. Remove the spray nozzle unit by gently pulling upward. **(See Figure K).** Remove the purple dust cap and place only the spray nozzle unit in warm water to soak. **(See Figure L)**
Figure K

See Figure L



Step 14. After soaking the spray nozzle tip for 15 minutes, rinse the spray nozzle unit and purple dust cap with warm water and allow them to dry completely. **(See Figure M**Error! Reference source not found.**)**

Figure M

Step 15. Place the purple dust cap back on the spray nozzle tip and put it back on the bottle. (See Figure N)

Figure N

Step 16. After following the steps to clear your blocked spray nozzle tip see "Priming your RYALTRIS® pump before use" section above and re-prime using 2 sprays. Replace the purple dust cap, and your RYALTRIS®is ready for use.
Repeat the unblocking steps if needed.**Do not leave Ryaltris openly in car or office or home in cold or hot weather.**
Keep track of the number of days you use RYALTRIS Even if the bottle seems to have medicine left in it, you may not receive the correct dose.

Overdose:
With the nasal route of administration overdose reactions are not anticipated.
If a child accidentally swallows RYALTRIS® or you use too much RYALTRIS®, call your doctor or go to the nearest hospital emergency room right away.

If you think you have taken too much RYALTRIS® contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, the next dose should be taken when it is due. Do not take a double dose.
What are possible side effects from using RYALTRIS ®?
These are not all the possible side effects you may feel when taking RYALTRISTM. If you experience any side effects not listed here, contact your healthcare professional.

- Sleepiness or drowsiness
- Unpleasant taste
- Nasal problems, which may include the following:
  - crusting in the nose
  - runny nose
  - nasal discomfort
- Slow wound healing. You should not use RYALTRIS® until your nose has healed if you have a sore in your nose, if you have had surgery on your nose, or if your nose has been injured.
- Slowed or delayed growth in children. A child's growth should be checked regularly while using RYALTRIS ®

Serious side effects and what to do about them		
	Talk to your healthcare professional	Stop taking drug

Symptom / effect	Only if severe	In all cases	and get immediate medical help
COMMON			
Nosebleeds	√		
RARE Nasal septal perforation (hole in the cartilage between your nose): a whistling sound when you breathe may be a symptom of nasal septal perforation.		√	
Thrush (*Candida*), a fungal infection in your nose and throat: any redness or white-colored patches in your nose or mouth.		√	
Cataracts: glare, reduced vision.		√	
Glaucoma: increased pressure in your eyes, eye pain.			√
Infection: fever, aches or pains, chills, feeling tired.		√	
Adrenal insufficiency: tiredness, weakness, nausea, vomiting, low blood pressure		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Storage:

Store upright with dust cap below 30°C. Do not freeze or refrigerate.
Keep out of reach and sight of children.

Last Revised: November 2023

PRODUCT REGISTRATION HOLDER

Glenmark Pharmaceuticals (Malaysia) Sdn Bhd (660397-W)

D-31-02, Menara Suezcap 1, No. 2, Jalan Kerinchi 59200 Kuala Lumpur Malaysia.