SAME SIZE ARTWORK
LEAFLET SIZE : 380 mm x 320 mm
FOLDING SIZE: 31.6 mm x 160 mm

31.6 mm

25 mm

320 mm

380 mm

SPACE FOR PHARMACODE

For the use of registered medical practitioner or a hospital or a laboratory

Ryaltris®

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

QUALITATIVE AND QUANTITATIVE 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	20mcg

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

DESCRIPTION

A white homogenous suspension free of lumps, crimp-sealed with a nasal spray pump and fitted with a white actuator and purple overcap. The bottle is free of residue, stains, cracks, dents, discolouration or flash or other visible defects.

PHARMACEUTICAL FORM

Nasal Spray, Suspension

CLINICAL PARTICULARS

INDICATIONS

RYALTRIS® is indicated for the treatment of moderate to severe symptoms associated with allergic rhinitis and rhinoconjunctivitis in patients 12 years of age and older.

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

Clinical Trials

Adolescents and Adults (12 years of age and older)
The efficacy and safety of RYALTRIS® in adults and adolescents 12 years of age and older with allergic rhinitis were evaluated in 4 studies (GSP 301-201, GSP 301-301, GSP 301-303 and GSP 301-304).

2-weeks studies
Three (GSP 301-201, GSP 301-301 and GSP 301-304) studies were similarly designed randomized, multicenter, double-blind, placebo- and active-controlled studies with a 2 -week duration in 2971 seasonal allergic rhinitis subjects. The population of the studies was 12 to 87 years of age (64.3% female, 35.7% male).

Patients were randomized to 1 of 4 treatment groups: 2 sprays per nostril twice daily of RYALTRIS®, olopatadine hydrochloride nasal spray, mometasone furoate nasal spray, and vehicle (pH 3.7) placebo. The olopatadine hydrochloride and mometasone furoate comparators used the same device and vehicle as RYALTRIS® but are not commercially marketed. Assessment of efficacy was based on the patient-reported reflective total nasal symptom score (rTNSS), instantaneous total nasal symptom score (iTNSS), and reflective and instantaneous total ocular symptom score (rTOSS and iTOSS, respectively). The rTNSS and iTNSS were calculated as the sum of the patient-reported symptom scores of 4 individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) on a 0 to 3 categorical severity scale (0=absent, 1=mild, 2=moderate, and 3=severe). Similarly, rTOSS and iTOSS were calculated using the 3 eye-related, non-nasal symptoms of itching/burning eyes, tearing/watering eyes, and redness of eyes using the same severity scale. Patients were required to record symptom severity daily (morning [AM] and evening [PM]), reflecting over the previous 12 hours (reflective) or at the time of recording (instantaneous). The primary efficacy endpoint was the mean change from baseline in average AM and PM patient-reported 12-hour rTNSS over the 2-week treatment period. The average AM and PM rTNSS (maximum score of 12) was assessed as the change from baseline for each day and then averaged over a 2-week treatment period.

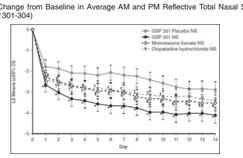
Across the studies, treatment with RYALTRIS® resulted in a statistically significant improvement in rTNSS compared with placebo. Results of the primary efficacy endpoint from the studies are shown in Table 1. Representative results from Study GSP 301-304 and GSP 301-301 are shown in Figure 1 and Figure 2.

Table 1: Mean Change from Baseline in Reflective Total Nasal Symptom Scores Over 2 Weeks* in Adults and Adolescents ≥ 12 Years with Seasonal Allergic Rhinitis

Study	Parameters	RYALTRIS®	Placebo	Olopatadine HCl nasal spray‡	Mometasone furoate nasal spray‡
GSP 301-201	N	157	158	160	159
	LS mean BL	10.4	10.3	10.3	10.5
	LS mean overall change from BL	-2.58	-1.41	-2.09	-1.87
	p-value† vs RYALTRIS®	--	<0.0001	0.0488	0.0043
GSP 301-301	N	299	283	294	294
	LS mean BL	10.1	10.2	10.3	10.2
	LS mean overall change from BL	-3.48	-2.50	-2.87	-3.09
	p-value† vs RYALTRIS®	--	<0.0001	0.0029	0.0587
GSP 301-304	N	291	290	290	293
	LS mean BL	10.09	10.32	10.16	10.20
	LS mean overall change from BL	-3.52	-2.44	-3.08	-3.05
	p-value† vs RYALTRIS®	--	<0.001	0.028	0.019
Pooled	N	747	731	744	746
	LS mean overall change from BL	-3.30	-2.36	-2.93	-2.89
	p-value† vs RYALTRIS®	--	<0.0001	0.0019	0.0005

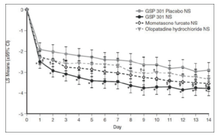
BL (Baseline)
* Average of AM and PM rTNSS for each day (maximum score = 12) and averaged over the 2-week treatment period.
† Statistically significant difference (p<0.05) using a gatekeeping strategy
‡ Not commercially marketed
Least Square (LS) Means and p-values were based on the mixed model repeated measures model, adjusting for covariates that included treatment, site, baseline 12-hour reflective total nasal symptom score, and study day as the within-patient effect.

Figure 1: LS Means of Change from Baseline in Average AM and PM Reflective Total Nasal Symptom Score (Full Analysis Set) (Study GSP 301-304)



AM = morning; LS = least square; NS = nasal spray; PM = evening.
†/‡* Indicate a significant difference when compared with placebo (p<0.05)

Figure 2: LS Means of Change from Baseline in Average AM and PM Reflective Total Nasal Symptom Score (Full Analysis Set) (Study GSP 301-301)

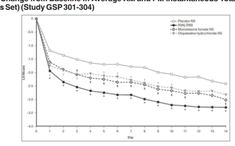


AM = morning; CI = confidence interval; LS = least-squares; NS = nasal spray; MMRM = mixed-effect model for repeated measures; PM = evening. †/‡* Statistically significant difference versus placebo (p<0.05). LS means, 95% CIs, and p values are based on MMRM model with change from baseline as dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-subject effect.

In these studies, RYALTRIS® also demonstrated statistically significant improvement in iTNSS as compared with placebo and demonstrated statistically significant improvements compared with placebo for each of the 4 individual nasal symptoms evaluated as rTNSS (p<0.05) and iTNSS (p<0.05).

Representative results from Study GSP 301-304 are shown in Figure 3.

Figure 3: LS Means of Change from Baseline in Average AM and PM Instantaneous Total Nasal Symptom Score for Each Day (Full Analysis Set) (Study GSP 301-304)



AM = morning; CI = confidence interval; LS = least square; NS = nasal spray; PM = evening.
†/‡* Indicate a significant difference when compared with placebo (p<0.05).

RYALTRIS® demonstrated statistically significant improvement compared with placebo in the change from baseline in average AM and PM patient-reported 12-hour rTOSS and iTOSS over a 2-week treatment period.

Following the initial dose, marked improvement in iTNSS has been observed over the first week and was sustained through two weeks of treatment.

The subjective impact of seasonal allergic rhinitis on a patient's health-related quality of life was evaluated by the Rhinoconjunctivitis Quality of Life Questionnaire - Standardized Activities (RQLQ[S]) [28 questions in 7 domains [activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional] evaluated on a 7-point scale, in which 0=no impairment and 6=maximum impairment). An overall RQLQ(S) score is calculated from the mean of all items in the instrument. The LS mean difference in the overall RQLQ(S) from baseline between RYALTRIS® and placebo was -0.56 [95% CI: -0.95, -0.18] in Study GSP 301-201, -0.43 [95% CI: -0.64, -0.21] in Study GSP 301-301 and -0.45 [95% CI: -0.68, -0.22] in Study GSP 301-304.

52-week study
The fourth study of RYALTRIS® (GSP 301-303), was a double-blind, randomised, placebo- controlled 52-week safety and efficacy study in subjects with perennial allergic rhinitis. It evaluated 24-hour (AM) rTNSS and iTNSS as secondary endpoints. Compared with placebo nasal spray pH 3.7, treatment with RYALTRIS® (n=391) resulted in statistically significant improvement in the change in average AM patient-reported rTNSS and iTNSS over the first 6, 30, and 52 weeks vs baseline.

Table 2: Mean Change from Baseline in Average AM Reflective Total Nasal Symptom Score over the First 6, 30, and 52 Weeks of Treatment (Full Analysis Set)

Week	Number of subjects (n) (RYALTRIS®, Placebo)	RYALTRIS® Treatment Effect Difference vs placebo		
		LS Mean	95% CI	P-value‡
6 weeks	391, 99	-0.81	(-1.29, -0.32)	0.0012
30 weeks	391, 99	-0.96	(-1.41, -0.50)	<0.0001
52 weeks	391, 99	-0.91	(-1.35, -0.47)	<0.0001

‡Statistically significant difference (p<0.05) using repeated measures analysis
CI = confidence interval; LS = least square; MMRM = mixed model repeated measures; NS = nasal spray LS Means, 95% confidence intervals, and p-values are based on separate MMRM models for each week assessment, with change from baseline as dependent variables, treatment group and site as fixed effect, baseline as covariate, and week as the within-subject effect.

Table 3 : Mean Change from Baseline in Average AM Instantaneous Total Nasal Symptom Score over the First 6, 30, and 52 Weeks of Treatment (Full Analysis Set)

Week	Number of subjects (n) (RYALTRIS®, Placebo)	RYALTRIS® Treatment Effect Difference vs placebo		
		LS Mean	95% CI	P-value‡
6 weeks	391, 99	-0.66	(-1.12, -0.20)	0.0053
30 weeks	391, 99	-0.83	(-1.26, -0.39)	0.0002
52 weeks	391, 99	-0.75	(-1.17, -0.33)	0.0005

‡Statistically significant difference (p<0.05) using repeated measures analysis
CI = confidence interval; LS = least square; MMRM = mixed model repeated measures; NS = nasal spray LS Means, 95% confidence intervals, and p-values are based on separate MMRM models for each week assessment, with change from baseline as dependent variables, treatment group and site as fixed effect, baseline as covariate, and week as the within-subject effect.

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 (C_{max}) 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 (AUC_{tau}) 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 (MI) 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 limited extent, into the urine.

Special Populations
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 C_{max} 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 m^2). 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.

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).

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 Qualitative and Quantitative Composition.
- Have untreated fungal, bacterial, or tuberculosis infections of the respiratory tract.

WARNINGS AND PRECAUTIONS

Driving and Operating Machinery
Due to the potential occurrence of somnolence, due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.
Caution is required if RYALTRIS® is used concomitantly with alcohol or other CNS depressants.
Somnolence has been reported following administration of RYALTRIS® in 2 out of 789 subjects taking RYALTRIS® in the clinical studies.

Local Nasal Effects
In clinical trials of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients treated with RYALTRIS® than those who received placebo

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.

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.

Hypercorticism and adrenal suppression may occur when nasal corticosteroids, including RYALTRIS®, are misused by taking higher-than-recommended dosages.

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

Hypersensitivity Reactions
Hypersensitivity reactions can occur with RYALTRIS®. Hypersensitivity reactions including wheezing, have occurred after the nasal administration of mometasone furoate. Discontinue RYALTRIS® if such reactions occur.

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.

Fertility, pregnancy and lactation

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/m^2 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/m^2 basis.

Mometasone furoate administered subcutaneously to rats at doses of approximately 1-fold the MRHDID on mg/m^2 basis, respectively did not result in impairment of fertility.

Pregnancy
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/m^2 basis, respectively. However, rats treated at approximately 120-fold and rabbits treated at approximately 1600-fold the MRHDID on mg/m^2 basis during the organogenesis showed a decrease in live fetuses (see NON-CLINICAL 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 NON-CLINICAL TOXICOLOGY).

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. Infants born of mothers who received corticosteroids during pregnancy should be observed carefully for hypoadrenalism.

Lactation
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.

SPECIAL POPULATIONS

Pediatrics
The safety and efficacy of RYALTRIS® in children under 12 years of age have not been established. No data are available.

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients, particularly at high doses prescribed for prolonged periods of time. Routinely monitor the growth of pediatric patients receiving RYALTRIS®. A placebo-controlled clinical trial in which paediatric patients were administered 100 micrograms of mometasone furoate nasal spray daily for one year did not observe a reduction in growth velocity. Periods of treatment greater than one year have not been studied.

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 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 4 - 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 casepatients 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

Adolescents and Adults (12 years of age and older)

Clinical Trials
The safety of RYALTRIS® in adult and adolescents 12 years of age and older was investigated in 3062 subjects (36.1% male and 63.9% female) with seasonal allergic rhinitis and 593 subjects (31.7% male and 68.3% female) with perennial allergic rhinitis.

In the placebo- and active- controlled, double-blind randomised clinical studies of 2-week duration in subjects with seasonal allergic rhinitis, the overall incidence of treatment emergent adverse events (TEAEs) was 13.9% in the RYALTRIS® treatment group, 13.2% in the olopatadine hydrochloride nasal spray treatment group, 7.9% in the mometasone furoate nasal spray treatment group, and 9.5% in the placebo treatment groups. Overall, <1% of patients in all treatment groups discontinued due to adverse reactions. Table 5 lists treatment-emergent adverse events reported with frequencies ≥1% and more frequently than placebo in patients treated with RYALTRIS® in the 2-week SAR studies.

Table 5: Most Frequently Reported Treatment Emergent Adverse Events with ≥1% Incidence That Were Reported More Frequently with RYALTRIS Than Placebo in the 2-Week Placebo- and Active-controlled Studies in Adult and Adolescent Patients with Seasonal Allergic Rhinitis

System Organ Class	Adverse Event Preferred Term	RYALTRIS® N = 789* n (%)†	Olopatadine HCl Nasal Spray* N = 751* n (%)†	Mometasone Furoate Nasal Spray* N = 746* n (%)†	Placebo N = 776* n (%)†
Nervous system disorder	Dysgeusia	24 (3.0)	16 (2.1)	0 (0)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	Epistaxis	8(1.0)	11 (1.5)	6 (0.8)	5 (0.6)
	Nasal discomfort	8(1.0)	4 (0.3)	4 (0.5)	6 (0.8)

* N = Total number of subjects in each treatment group in the safety analysis set
† n = number of subjects with adverse events in each MedDRA term; Number (%) of subjects with adverse events (AEs), sorted on international order for system organ class (SOC) and alphabetically for preferred term (PT). Percentages are based on total number of subjects in the safety set within each treatment group. At each level of summation (overall, SOC, PT), subjects are only counted once.
* Not commercially marketed

The safety data described below reflect exposure to RYALTRIS® in 789 patients with seasonal allergic rhinitis in clinical studies of 2-week duration. The adverse reactions are listed below by system organ class and frequency.

Frequencies are defined as:

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)

Nervous system disorder
Common: dysgeusia (unpleasant taste).
Uncommon: dizziness, headaches, lethargy, somnolence, insomnia.

Respiratory, thoracic and mediastinal disorders
Uncommon: epistaxis, nasal dryness, nasal discomfort, nasal inflammation, oropharyngeal pain, throat irritation, sneezing.

Gastrointestinal disorders
Uncommon: dry mouth, abdominal pain.

General disorders and administration site conditions
Uncommon: Fatigue

In the double-blind, placebo-controlled, 52-week study (Study GSP 301-303), subjects with perennial allergic rhinitis were randomised to receive RYALTRIS® (pH 3.7), a placebo nasal spray pH 3.7, or a placebo nasal spray pH 7.0 administered as 2 sprays/nostril twice daily (morning [AM] and evening [PM]). The safety profile in the long-term perennial allergic rhinitis study was comparable with the 2-week seasonal allergic rhinitis studies.

Additionally, improvement in nasal symptoms was observed over the 52-week treatment duration.

Overall, the incidence of treatment-related TEAEs was 51.7% in the RYALTRIS® treatment group, 41.4% in the placebo nasal spray pH 3.7 treatment group, and 53.5% in the placebo nasal spray pH 7.0 treatment group. Of the 593 treated patients, 3.8% of patients receiving RYALTRIS® discontinued from the study due to an adverse event, compared with 2.0% and 3.0% of patients receiving placebo nasal spray pH 3.7 and pH 7.0, respectively. Table 6 lists TEAEs reported with frequencies ≥1% that were more frequent for RYALTRIS® than Placebo pH3.7.

Table 6: Treatment Emergent Adverse Events with ≥1% Incidence that Were Reported More Frequently with RYALTRIS® than Placebo in the 52-Week Study in Adult and Adolescent Patients with Perennial Allergic Rhinitis

System Organ Class	Adverse Event Preferred Term	RYALTRIS® (N=393) N (%)	Placebo Nasal Spray, pH 3.7 N = 99 n (%)	Placebo Nasal Spray, pH 7.0 N = 101 n (%)
Infections and infestations	Upper respiratory	25 (6.4)	6 (6.1)	9 (8.9)
	Urinary tract infection	9 (2.3)	2 (2.0)	0 (0.0)
	Viral upper respiratory tract	9 (2.3)	2 (2.0)	3 (3.0)
Respiratory, thoracic and mediastinal disorders	Epistaxis	18 (4.6)	2 (2.0)	2 (2.0)
	Nasal discomfort	11 (2.8)	2 (2.0)	5 (5.0)
	Cough	9 (2.3)	2 (2.0)	2 (2.0)
	Bronchitis	5 (1.3)	0 (0.0)	2 (2.0)
	Pharyngitis streptococcal	5 (1.3)	0 (0.0)	2 (2.0)
Nervous system disorder	Dysgeusia	8 (2.0)	0 (0.0)	1 (1.0)
	Headache	16 (4.1)	3 (3.0)	5 (5.0)
Musculoskeletal	Back pain	5 (1.3)	0 (0.0)	3 (3.0)
Gastrointestinal	Nausea	5 (1.3)	1 (1.0)	2 (2.0)
Injury, poisoning and procedural complications	Procedural pain	6 (1.5)	1 (1.0)	2 (2.0)

In the RYALTRIS® treatment group of the 52-week study, 16 (4.1%) patients experienced mild epistaxis, and 2 (0.5%) patients experienced moderate epistaxis. In the placebo treatment groups, 2 (2.0%) patients in each placebo treatment group experienced mild epistaxis, and no placebo patients experienced moderate epistaxis. No incidents of severe epistaxis were reported in any treatment group. Focused nasal examinations were performed, and no nasal ulcerations were observed.

The following additional adverse reactions have been reported in post-marketing use with mometasone furoate aqueous nasal spray: vision blurred.

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.

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 mometasone furoate nasal spray, 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.

PE00000 **SG**

ICONGRAPHICS CODE:

PANTONE SHADE

PANTONE BLACK PROCESS C

Supersedes Artwork Code: PE62231

PHARMACODE:

SAME SIZE ARTWORK
LEAFLET SIZE : 380 mm x 320 mm
FOLDING SIZE: 31.6 mm x 160 mm

25 mm

320 mm

380 mm

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 tumorigenic potential in mice at oral doses up to 500 mg/kg/day (approximately 510-fold the MRHDID on mg/m^2 basis) for 78 weeks or in rats at oral doses up to 200 mg/kg/day (approximately 410-fold the MRHDID on a mg/m^2 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/m^2 basis). No effect on fertility was observed at an oral dose of 50 mg/kg/day (approximately 100-fold the MRHDID on a mg/m^2 basis).

In an oral embryofetal development study, pregnant rats were dosed throughout the period of organogenesis at doses up to 600 mg/kg/day. Maternal toxicity, producing death and reduced maternal body weight gain was observed at 600 mg/kg/day (approximately 1200 times the MRHDID on a mg/m^2 basis). Olopatadine produced cleft palate at 60 mg/kg/day (approximately 120 times the MRHDID on a mg/m^2 basis) and decreased embryo-fetal viability and reduced fetal weight in rats at 600 mg/kg/day (approximately 1200 times the MRHDID on a mg/m^2 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 400 mg/kg/day (approximately 1600-fold the MRHDID on a mg/m^2 basis).

In peri-/post-natal toxicity studies, pregnant rats received oral doses of olopatadine up to 600 mg/kg/day during late gestation through the lactation period. Olopatadine produced decreased neonatal survival at 60 mg/kg/day (approximately 120 times the MRHDID on a mg/m^2 basis) and reduced body weight gain in pups at 4 mg/kg/day (approximately 7 times the MRHDID on a mg/m^2 basis). These effects appeared attributable to exposure of pups via the milk as demonstrated in a cross-fostered study in which pups of untreated dams cross-fostered to dams treated with 60 mg/kg/day olopatadine orally during the lactation period exhibited decreased body weight gain.

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. At 15 mcg/kg (approximately equivalent to the MRHDID on a mcg/m^2 basis), 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/m^2 basis, respectively), cleft palate in mice administered 180 mcg/kg subcutaneously (approximately 55- and 4-fold the MRHDID on body weight and mg/m^2 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/m^2 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

In-use shelf life after opening:
60 days

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 a actuator and overcap.
For 120 Metered Sprays:
20ml HDPE bottle crimp-sealed with a nasal spray pump and fitted with a actuator and overcap.
For 56 Metered Sprays:
20ml HDPE bottle crimp-sealed with a nasal spray pump and fitted with a actuator and overcap.

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

Product Owner:
GLENMARK SPECIALTY SA
AVENUE LEOPOLD-ROBERT 37, 2300 LA CHAUX-DE-FONDS SWITZERLAND

DATE OF REVISION OF THE TEXT
October 2022

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 moderate to severe symptoms of allergic rhinitis, ("hay fever" or other year round allergies) and rhinoconjunctivitis (allergy defined by symptoms in the nose and eyes) in patients 12 years of age and older.

How does RYALTRIS® work?
RYALTRIS® helps reduce the symptoms of allergies 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, carboxymethylcellulose 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 if RYALTRIS® will harm your unborn baby.
- Are breastfeeding or plan to breast-feed. It is not known if RYALTRIS® 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.

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)

How to take RYALTRIS®:
RYALTRIS® is for use in your nose only. Do not spray it into your eyes or mouth. Use RYALTRIS® exactly as recommended by your healthcare provider.
RYALTRIS® relieves the symptoms within 10 minutes. However, you will get the best results if you keep using RYALTRIS® 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).

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

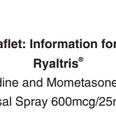
Priming your RYALTRIS® pump before first use
Before you prime the bottle, shake the bottle well.
Shake container well before each use. The bottle should be discarded after the labelled number of actuations

Diagram of RYALTRIS® nasal spray bottle (See Figure 1)
Note: The figures below are intended for illustrative purposes only. Thus, the product labels may not be representative of the actual drug product.

Figure 1

Step 1 - Remove the dust cap.
Remove the purple plastic dust cap from the spray pump tip of the bottle. (See Figure 2)

Figure 2



Step 2 - Preparing the nasal spray bottle
- Hold the nasal spray bottle firmly and upright with your index and middle finger on either side of the applicator (on finger rests) while supporting the grooved base of the bottle with your thumb.
- Before first use, push down on the pump quickly and firmly approximately 6 times, releasing the spray into the air, away from the eyes and face until a fine mist appears. (See Figure 3)
- 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.

Figure 3

Your RYALTRIS® is now ready for use.

Using your RYALTRIS®:

Step 3 -
Gently blow your nose to clear your nostrils. (See Figure 4)

Figure 4

Step 4 - Using the nasal spray:
- Shake the bottle well before each use (morning and evening).
- Hold the bottle firmly with your index and middle finger on either side of the applicator (on finger rests) while supporting the grooved base of the bottle with your thumb. (See Figure 5)

Figure 5

- Hold 1 nostril closed with a finger. Insert the end of the nasal tip into the other nostril, pointing it slightly toward the outside of the nose, away from the nasal septum (the wall between the 2 nostrils). (See Figure 6)

Figure 6

- Tilt your head forward slightly. Keep the bottle upright, and press down once quickly and firmly on the finger rests to activate the pump. Breathe in (inhale) gently through your nose as you spray. Then breathe out through your mouth. (See Figure 7)
- Try not to get any spray in your eyes or directly on your nasal septum (the wall between the 2 nostrils).
- Adults and Adolescents (12 years of age and older): Deliver 2 sprays in each nostril.

Figure 7

- Avoid blowing your nose for the next 15 minutes to make sure RYALTRIS® gets a chance to work. Do not tip your head back right after using to keep the medicine from going into your throat.
- After you finish using the medicine, each time wipe the tip with a clean dry tissue or cloth. (See Figure 8)

Figure 8

While holding the spray pump unit, each time push the dust cap back on the spray tip of the bottle until a noticeable click is observed. (See Figure 9)

Figure 9

How to clear the RYALTRIS® spray pump unit if it becomes clogged:
You must never attempt to unblock or enlarge the spray hole with a pin or other sharp object because this will destroy the spray mechanism and you may not get the correct dose of medicine. (see figure 10)

Figure 10

If the spray pump unit becomes blocked, remove it by gently pulling upward. (See Figure 11)

Figure 11

Remove the dust cap and place only the spray pump unit in warm water to soak. (see figure 12)

Figure 12

After soaking for approximately 15 minutes, rinse both ends with warm tap water for 1- 2 minutes and allow them to dry completely. (See Figure 13)

Figure 13

When dry, place the dust cap on the spray pump tip and put the spray pump unit back on the bottle.
(See Figure 14)

Figure 14

Following the unblocking procedure, review the "Priming your RYALTRIS® pump before use" section above and re-prime using 2 sprays. Replace the dust cap, and your RYALTRIS® is ready for use.

Repeat the unblocking steps if needed.

You should clean your nasal spray at least once a week to stop it from getting blocked up.
Additional cleaning is required when your spray becomes blocked.

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 RYALTRIS®. 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			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
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.

Manufactured by :
Glenmark
PHARMACEUTICALS LTD.
(Unit III), Village Kishanpura,
Baddi-Nalagarh Road,
Tehsil Baddi, Distt. Solan,
(H.P.) - 173 205, India.

Ryaltris® is a Registered Trademark of Glenmark Specialty S. A

PE00000 SG

ICONGRAPHICS CODE:

PANTONE SHADE

PANTONE BLACK PROCESS C

Supersedes Artwork Code: PE62231

PHARMACODE: