SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RYALTRIS

(Olopatadine Hydrochloride and Mometasone Furoate Nasal Spray 665 mcg/25 mcg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each spray delivers:

Olopatadine Hydrochloride USP equivalent to Olopatadine… 600 mcg
Mometasone Furoate Monohydrate equivalent to Mometasone Furoate. 25 mcg
Benzalkonium Chloride NF ....0.02 % w/w

Excipients… .....q.s.

For full list of excipients, please see *Section 6.1.*

3. PHARMACEUTICAL FORM

Nasal Spray, Suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

RYALTRIS is indicated for the treatment of symptoms associated with seasonal allergic rhinitis in patients 12 years of age and older.

4.2. Posology and method of administration Posology

Seasonal Allergic Rhinitis

The recommended dosage of RYALTRIS is 2 sprays in each nostril twice daily.

Method of administration

Administer RYALTRIS by the intranasal route only. 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.

Avoid spraying RYALTRIS into the eyes or mouth.

4.3. Contraindications

RYALTRIS is contraindicated in patients with known hypersensitivity to olopatadine hydrochloride, mometasone furoate, or any ingredients of RYALTRIS *listed in section 6.1.*

4.4. Special warnings and precautions for use

Local Nasal Effects

Instances of nasal ulceration and nasal septal perforation have been reported in patients following the intranasal application of antihistamines.

Instances of nasal septal perforation have been reported following the intranasal application of corticosteroids.

Instances of epistaxis have been reported in patients following the intranasal application of antihistamines and corticosteroids *[see Undesirable effects (4.8)]*.

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

In clinical studies with mometasone furoate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with RYALTRIS. Patients using RYALTRIS over several months or longer should be examined periodically for evidence of Candida infection or other signs of adverse effects on the nasal mucosa. There were no instances of Candida infection reported with RYALTRIS in the clinical studies *[see Undesirable effects (4.8)]*.

Visual disturbances, including Glaucoma, Cataract and Chorioretinal disorders

Nasal and inhaled corticosteroids may result in the development of glaucoma, cataracts, or rare diseases such as central serous chorioretinopathy (CSCR). Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, or cataract.

Hypersensitivity Reactions

Hypersensitivity reactions, including instances of wheezing, may occur after the intranasal administration of mometasone furoate monohydrate. Discontinue RYALTRIS if such reactions occur *[see Contraindications (4.3)]*.

Immunosuppression

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

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

Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects

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

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

Effect on Growth

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Routinely monitor the growth of pediatric patients receiving RYALTRIS *[see Use in Special Populations (5.2)]*.

Somnolence

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination, such as operating machinery or driving a motor vehicle, after administration of RYALTRIS. Concurrent use of RYALTRIS with alcohol or other central nervous system (CNS) depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Somnolence has been reported following administration of RYALTRIS in the clinical studies *[see Undesirable effects (4.8)]*.

Antihistamine effects

Concomitant use of olopatadine (e.g. eyes drops) or other antihistaminic drugs administered via nasal, ocular or oral route may increase the risk of antihistamine adverse effects.

Paediatric population

It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is maintained. In addition, consideration should be given to referring the patient to a paediatric specialist.

Excipients:

Ryaltris contains 0.02 mg benzalkonium chloride in each actuation. Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.

4.5. Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic 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 components taken individually, as no pharmacokinetic interaction between olopatadine and mometasone furoate was observed when administered in combination.

Olopatadine: Drug interactions with inhibitors of liver enzymes are not anticipated because olopatadine is eliminated predominantly by renal excretion. Olopatadine did not inhibit the in vitro metabolism of specific substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Based on these data, drug interactions involving P450 inhibition are not expected. Due to the modest protein binding of olopatadine (55%), drug interactions through displacement from plasma proteins are also not expected.

Mometasone Furoate: Studies have shown that mometasone furoate, a component of RYALTRIS, is primarily and extensively metabolized to multiple metabolites in the liver of all species investigated. In vitro studies have confirmed the primary role of cytochrome P450 (CYP) 3A4 in the metabolism of mometasone furoate. Concomitant administration of

RYALTRIS and CYP3A4 inhibitors may inhibit the metabolism, and increase the systemic exposure to mometasone furoate and potentially increase the risk of systemic corticosteroid side effects.
Caution should be exercised when considering the coadministration of RYALTRIS with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, cobicistat-containing products, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin). Consider the benefit of coadministration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side effects.

4.6. Fertility, pregnancy and lactation

Fertility

Olopatadine Hydrochloride: Olopatadine administered orally to male and female rats at dose of 400 mg/kg/day, (approximately 680 times the maximum recommended human dose [MRHD] for adults on a mg/m^2 basis) resulted in a decrease in the fertility index and reduced implantation rate. No effects on fertility were observed at a dose of 50 mg/kg/day (approximately 85 times the MRHD for adults on a mg/m^2 basis).

Mometasone Furoate: In rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (less than the maximum recommended daily intranasal dose [MRDID] in adults on a mcg/m^2 basis).

Pregnancy

Risk Summary

There are no adequate and well-controlled clinical studies with RYALTRIS, olopatadine hydrochloride only, or mometasone furoate only in pregnant women. No animal reproductive and developmental studies have been conducted with RYALTRIS. Animal reproductive and developmental studies have been conducted with olopatadine when administered orally and with mometasone furoate when administered subcutaneously, orally, or topically by dermal route. The animal studies revealed evidence of treatment-related effects on fetuses and pups following systemic exposure to olopatadine hydrochloride or mometasone furoate. Malformations in animals following systemic exposure to mometasone furoate are consistent with the known effects of corticosteroids.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Since animal reproduction studies are not always predictive of human response, RYALTRIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Data

Animal Data

No reproductive toxicology studies were conducted with RYALTRIS; however, studies are available for the individual active components, olopatadine hydrochloride and mometasone furoate, as described below.

Olopatadine was not teratogenic in rabbits and rats at oral doses of up to 400 or 600 mg/kg/day, respectively (approximately 1400 and 1000 times the MRHD for adults on a mg/m^2 basis, respectively). However, a decrease in the number of live fetuses was observed in rabbits at the oral olopatadine doses of 25 mg/kg (approximately 88 times the MRHD for adults on a mg/m^2 basis) and above, and in rats at oral doses of 60 mg/kg (approximately 100 times the MRHD for adults on a mg/m^2 basis) and above. In rats, viability and body weights of pups were reduced on Day 4

postpartum at the oral doses of 60 mg/kg (approximately 100 times the MRHD for adults on a mg/m^2 basis) and above, but no effect on viability was observed at the dose of 20 mg/kg (approximately 35 times the MRHD for adults on a mg/m^2 basis).

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (less than the MRDID in adults on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately 2 times the MRDID in adults on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 10 times the MRDID in adults on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 6 times the MRDID in adults on a mcg/m^2 basis) produced delays in ossification but no malformations.

In rabbits, mometasone furoate caused multiple malformations (e.g., flexed front paws, gallbladder agenesis, umbilical hernia, and hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 6 times the MRDID in adults on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly or domed head) at 700 mcg/kg (approximately 30 times the MRDID in adults on a mcg/m^2 basis). At 2800 mcg/kg (approximately 110 times the MRDID in adults on a mcg/m^2 basis), most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (approximately 6 times the MRDID in adults on a mcg/m^2 basis).

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis).

Breast-feeding

Risk Summary

It is not known whether RYALTRIS is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when RYALTRIS is administered to a nursing woman.

Clinical Considerations

Since there are no data from well-controlled human studies on the use of RYALTRIS by nursing mothers, based on data from the individual components, RYALTRIS should be used by nursing mothers only if the potential benefit to the patient outweighs the potential risks to the infant.

Data

Animal Data

Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical nasal administration could result in sufficient systemic absorption to produce detectable quantities in human breast milk.

4.7. Effects on ability to drive and use machines

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination, such as operating machinery or driving a motor vehicle, after administration of RYALTRIS.

4.8. Undesirable effects

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)

Frequency **System Organ Class**	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Nervous system disorder		Dysgeusia (unpleasant taste)	Dizziness Headaches Lethargy Somnolence Insomnia			
Respiratory, thoracic and mediastinal disorders			Epistaxis Nasal dryness Nasal discomfort Nasal Inflammation Oropharyngeal pain Throat irritation Sneezing			
Gastrointestinal disorders			Dry mouth Abdominal pain			
General disorders and administration site conditions			Fatigue			

In a long term safety clinical study (52 weeks of study treatment), 593 patients with perennial allergic rhinitis were randomized to receive RYALTRIS or placebo. The most frequently reported adverse reactions with RYALTRIS (≥2%, and greater than the placebo treatment group) were upper respiratory tract infection, epistaxis, headache, nasal discomfort, viral upper respiratory tract infection, urinary tract infection, cough, and dysgeusia.

Systemic and local corticosteroid use may result in the following:

- Nasal ulcerations, nasal septal perforations, epistaxis, impaired wound healing, and *Candida albicans* infection *[see Special warnings and precautions for use (4.4)]*
- Glaucoma, cataracts and chorioretinal disorder *[see Special warnings and precautions for use (4.4)]*
- Immunosuppression *[see Special warnings and precautions for use (4.4)]*
- HPA axis effects, including growth reduction *[see Special warnings and precautions for use (4.4)], [Use in Special Populations (5.2)]*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 to TMDA.

4.9. Overdose

There have been no reported overdosages with RYALTRIS. Accordingly, no data on the effects of acute or chronic overdosage with RYALTRIS are available. RYALTRIS contains both olopatadine hydrochloride and mometasone furoate; therefore, the risks associated with overdosage for the individual components described below apply to RYALTRIS.

Acute overdosage with this dosage form is unlikely since one 30-day (240 metered doses) bottle of RYALTRIS contains approximately 160 mg of olopatadine hydrochloride and 6 mg of mometasone furoate.

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 olopatadine hydrochloride. Should overdose occur, symptomatic or supportive treatment is recommended, taking into account any concomitantly ingested medications.

No mortality was observed in rats at an intranasal dose of 3.6 mg/kg (approximately 6 times the MRHD for adults and adolescents ≥12 years of age and 7 times the MRHD for children 6- 11 years of age on a mg/m^2 basis) or in dogs at an oral dose of 5 g/kg (approximately 28000 times the MRHD for adults and adolescents ≥12 years of age and 33000 the MRHD for children 6-11 years of age on a

mg/m^2 basis). The oral median lethal dose in mice and rats were 1490 and 3870 mg/kg, respectively (approximately 1200 and 6500 times the MRHD for adults and adolescents ≥12 years of age and 1500 and 7700 times the MRHD for children 6-11 years of age, on a mg/m^2 basis, respectively).

Mometasone Furoate: Because of low systemic bioavailability and an absence of acute drug related systemic findings in clinical studies, overdose is unlikely to require any therapy other than observation. Intranasal administration of 1600 mcg (8 times the recommended daily dose of mometasone furoate from RYALTRIS) daily for 29 days in healthy human volunteers showed no increased incidence of adverse events. Single intranasal doses up to 4000 mcg and oral inhalation doses up to 8000 mcg have been studied in human volunteers, with no adverse effects reported. Chronic overdosage with any corticosteroid may result in signs or symptoms of hypercorticism [see Special warnings and precautions for use (4.4)].

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Decongestants and other nasal preparations for topical use
ATC Code: R01AD

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 corticosteroid demonstrating potent anti-inflammatory properties. The precise mechanism of corticosteroid action on allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Pharmacodynamic effects

Cardiac Effects

A study specifically designed to evaluate the effect of RYALTRIS on the QT interval has not been conducted.

HPA Axis Effect

A study specifically designed to evaluate the effect of RYALTRIS on the HPA axis has not been conducted.

Glenmark Clinical Study

Adult and Adolescent Patients Aged 12 Years and Older

The efficacy and safety of RYALTRIS in adults and adolescents 12 years of age and older

with seasonal allergic rhinitis were evaluated in 2 similarly designed randomized, multicenter, double-blind, placebo-controlled, safety and efficacy clinical studies (Studies 1 and 2) with a 2 -week duration in 2356 randomized patients. The population of Study 1 (GSP 301-304) was 12 to 82 years of age (62.9% female, 37.1% male; 81.6% white, 15.4% black, 1.9% Asian, and 1.1% other). The demographics in Study 2 (GSP 301-301) were similar.

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 dosing (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 2 studies, treatment with RYALTRIS resulted in a statistically significant improvement in rTNSS compared with placebo. Representative results from Study 1 are shown in Table 1 and Figure 1.

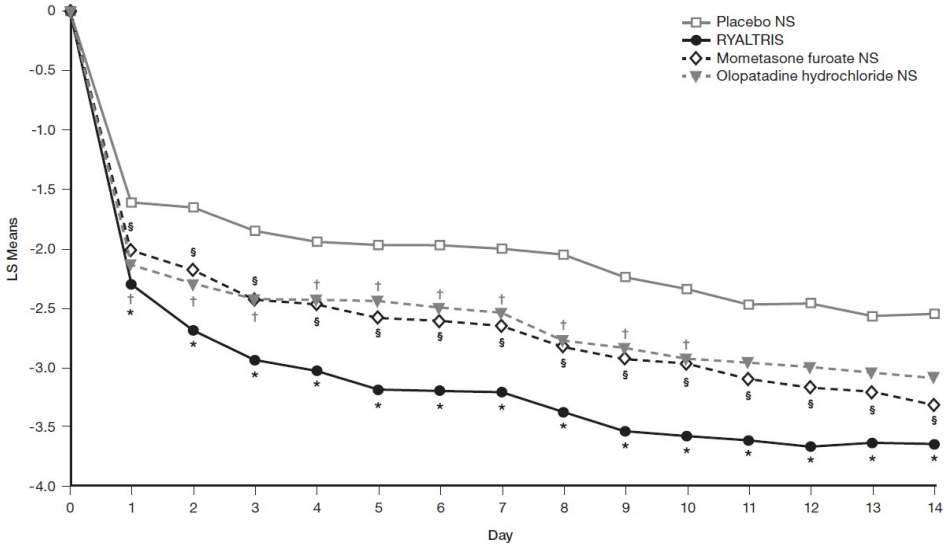
Table 1: Mean Change from Baseline in Reflective Total Nasal Symptom Scores Over 2 Weeks* in Adults and Adolescents Aged ≥ 12 Years with Seasonal Allergic Rhinitis in Study 1 (Full Analysis Set)

		Baseline	**Change From Baseline**	**RYALTRIS Treatment Effect Difference**		
Treatment (2 sprays/nostril twice daily)	N	Mean	LS Mean	LS Mean	95% CI	P-value†
RYALTRIS	291	10.09	-3.52	--	--	--
Olopatadine HCl nasal spray‡	290	10.16	-3.08	-0.44	(-0.84, -0.05)	0.028

Mometasone furoate nasal spray‡	293	10.20	-3.05	-0.47	(-0.86, -0.08)	0.019
Placebo	290	10.32	-2.44	-1.09	(-1.49, -0.69)	<0.001

* 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.
‡ Non-commercially marketed
Least Square (LS) Means, 95% Confidence Intervals (CIs), 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: Least Square Means of Change from Baseline in Average AM and PM Reflective Total Nasal Symptom Score for Each Day (Full Analysis Set) (Study 1)

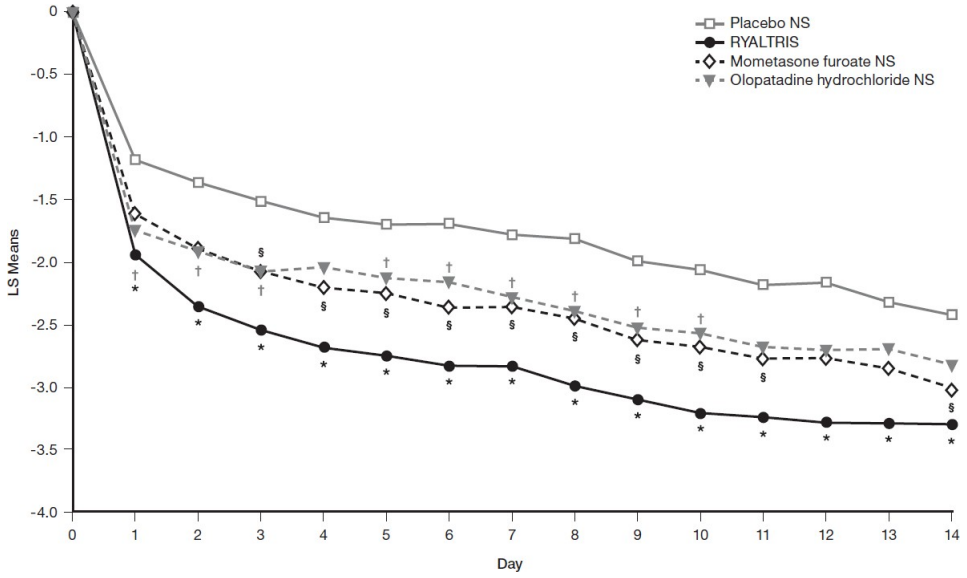


AM = morning; NS = nasal spray; PM = evening.
†§* Indicate a significant difference when compared with placebo (p<0.05)

RYALTRIS demonstrated statistically significant improvements compared with placebo for each of the 4 individual nasal symptoms evaluated as rTNSS.

In these studies, RYALTRIS also demonstrated statistically significant improvement in iTNSS as compared with placebo (Study 1 LS mean difference: -1.49, p<0.001). Representative results from Study 1 are shown in
Figure 2.

Figure 2: Least Square Means of Change from Baseline in Average AM and PM Instantaneous Total Nasal Symptom Score for Each Day (Full Analysis Set) (Study 1)



AM = morning; NS = nasal spray; PM = evening.
†§* Indicate a significant difference when compared with placebo ($p<0.05$)

RYALTRIS demonstrated statistically significant improvements compared with placebo for each of the 4 individual nasal symptoms evaluated as iTNSS.

RYALTRIS demonstrated statistically significant improvement compared with placebo in the change from baseline in average AM and PM patient-reported 12-hour rTOSS (Study 1 LS mean difference: -0.52, p=0.001) and iTOSS (Study 1 LS mean difference: -0.50, p=0.001) over a 2-week treatment period.

Onset of action was observed within 15 minutes, defined as the first time point after initiation of treatment when RYALTRIS demonstrated a statistically significantly greater change from baseline in iTNSS compared with placebo. Following the initial dose, iTNSS improved markedly over the first week and was sustained through 2 weeks of treatment (Figure 2).
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=not troubled and 6=extremely troubled). An overall RQLQ(S) score is calculated from the mean of all items in the instrument. A change from baseline of at least 0.5 points is considered a clinically meaningful improvement. In each of these studies, treatment with RYALTRIS resulted in a statistically significant greater decrease from baseline in the overall RQLQ(S) than placebo (Study 1 LS mean difference: -0.45 [95% CI: -0.68, -0.22]). In these studies, the treatment differences between RYALTRIS and placebo were less than the minimum important difference of 0.5 points.

In addition, a double-blind, randomized, placebo-controlled, 52-week, safety and efficacy study in patients with perennial allergic rhinitis evaluated 24-hour (AM) rTNSS and iTNSS as secondary endpoints. Treatment with RYALTRIS (n=391) resulted in statistically significant improvement in change from baseline in average AM patient-reported rTNSS and iTNSS over the first 6, 30, and 52 weeks compared with placebo nasal spray pH 3.7 (n=99).

Focused nasal examinations were performed, and no nasal ulcerations were observed.

2. Pharmacokinetic properties

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*hr/mL for olopatadine and 58.40 ± 27.00 pg*hr/mL 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 reported as 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 [^{14}C] 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, 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 [^{14}C] 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.

Following intravenous administration, the effective plasma elimination half-life of mometasone furoate was 5.8 hours. Any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.

Special Populations

No pharmacokinetic studies were performed in special populations with RYALTRIS. The pharmacokinetics of the combination of olopatadine and mometasone furoate is expected to reflect that of the individual components, as the pharmacokinetics of the combination was found to be comparable to the individual components.

Hepatic Impairment: For olopatadine, metabolism is a minor route of elimination. No specific pharmacokinetic study examining the effect of hepatic impairment was conducted.
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 Impairment: 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 AUC_{0-12} 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, 20mg 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.

Age: RYALTRIS pharmacokinetics has not been investigated in patients under 12 years of age *[Use in Special Populations (5.2)]*. 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.

Gender: Based on population pharmacokinetic analysis, the pharmacokinetics of olopatadine and mometasone furoate with RYALTRIS was not influenced by gender.

Race:. Based on population pharmacokinetic analysis, the pharmacokinetics of olopatadine and mometasone furoate with RYALTRIS was not influenced by race (white, American Indian or Alaska Native, Asian, black or African American, Native Hawaiian or other Pacific islander).

Pediatric Use

The safety and effectiveness of RYALTRIS in pediatric patients below the age of 12 years have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied.

The growth of pediatric patients receiving intranasal corticosteroids, including RYALTRIS, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risk/ benefits of noncorticosteroid treatment alternatives.

The potential of mometasone furoate nasal spray 50 mcg to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

Geriatric Use

No overall differences in safety or efficacy were observed in data collected from 145 patients aged 65 years and older versus younger patients who were treated with RYALTRIS in placebo- and active- controlled studies.

Hepatic Impairment

No studies have been conducted with RYALTRIS in patients with hepatic impairment. However, there have been reports of concentrations of mometasone furoate appearing to increase with severity of hepatic impairment.

3. Preclinical safety data

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with RYALTRIS; however, studies are available for the individual active components, olopatadine hydrochloride and mometasone furoate, as described below.

Olopatadine Hydrochloride: Olopatadine administered orally was not carcinogenic in mice and rats at doses of up to 500 and 200 mg/kg/day, respectively (approximately 420 and 340 times the MRHD for adults and adolescents ≥12 years of age and 500 and 400 times the MRHD for children 6-11 years of age by intranasal administration, respectively, on a mg/m^2 basis).
Olopatadine showed no evidence of genotoxicity in various in vitro and in vivo genotoxicity assays.

Mometasone Furoate: In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 1 and 2 times the MRDID in adults [400 mcg] and children [100 mcg], respectively, on a mcg/m^2 basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 2 times the MRDID in adults and children, respectively, on a mcg/m^2 basis).

Mometasone furoate increased chromosomal aberrations in an in vitro Chinese hamster ovary-cell assay but did not show any evidence of genotoxicity in other in vitro and in vivo genotoxicity assays.

6.0 PHARMACEUTICAL PARTICULARS:

1. List of excipients

- Microcrystalline Cellulose and Carboxymethyl cellulose sodium
- Dibasic Sodium Phosphate Heptahydrate
- Carboxymethyl Cellulose Sodium
- Sodium Chloride
- Benzalkonium Chloride Solution 50%
- Edetate Disodium
- Polysorbate 80
- Hydrochloric Acid
- Sodium Hydroxide
- Water for Injection

2. Incompatibilities

None Reported

3. Shelf life

24 Months

4. Special precautions for storage

Store upright with the dust cap below 30°C. Do not freeze or refrigerate.

5. Nature and contents of container and special equipment for use, administration or implantation

A printed carton containing a leaflet & a labelled white bottle containing 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.

240 Metered Sprays

29.0 g suspension filled in 30ml HDPE bottle crimp-sealed with a nasal spray pump and fitted with a actuator and overcap.

120 Metered Sprays

18.0 g suspension filled in 20ml HDPE bottle crimp-sealed with a nasal spray pump and fitted with a actuator and overcap.

56 Metered Sprays

9.0 g suspension filled in 20ml HDPE bottle crimp-sealed with a nasal spray pump and fitted with a actuator and overcap.

6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance

with local requirements.

7. MARKET AUTHORIZATION HOLDER:

Glenmark Specialty S.A.
Domiciled at NEUCHATEL SUIZA
Avenue Léopold-Robert 37, 2300 La Chaux-de-Fonds, Switzerland

Plant /Site: Glenmark Pharmaceuticals Limited
At: (Unit III), Village Kishanpura, Baddi-Nalagarh Road, Tehsil Baddi, Distt. Solan (H.P.)-173 205, India.

8. MARKET AUTHORIZATION NUMBER

TAN 22 HM 0477

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

05th December, 2022

10. DATE OF REVISION OF THE TEXT