NEW DRUG APPROVAL

Brand Name	Ryaltris™
Generic Name	olopatadine hydrochloride and mometasone furoate monohydrate
Drug Manufacturer	Glenmark Specialty

New Drug Approval

FDA approval date: January 13, 2022

Review designation: Standard

Type of review: Type 4 - New Combination; New Drug Application (NDA): 211746

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Allergic rhinitis (AR) is an atopic disease characterized by symptoms of nasal congestion, clear rhinorrhea, sneezing, postnasal drip, and nasal pruritis. It affects one in six individuals and is associated with significant morbidity, loss of productivity, and healthcare costs. Historically, AR was thought to be a disease process of the nasal airway alone. Still, the development of the unified airway theory has classified AR as a component of systemic allergic response, with other associated conditions, such as asthma and atopic dermatitis, sharing an underlying systemic pathology. AR can be classified as either seasonal (intermittent) or perennial (chronic), with approximately 20% of cases being seasonal, 40% perennial, and 40% with features of both. In addition to nasal symptoms, patients with AR may also present with associated allergic conjunctivitis, non-productive cough, Eustachian tube dysfunction, and chronic sinusitis. Once diagnosed, AR is treatable with a variety of modalities, with intra-nasal glucocorticoids being first-line therapy.

Epidemiology: Allergic rhinitis is common, affecting 10 to 30 percent of children and adults in the United States and other industrialized countries. It may be less common in some parts of the world, although even developing countries report significant rates. The prevalence of asthma, rhinoconjunctivitis, and eczema were systematically evaluated in approximately 1.2 million children in 98 countries in the International Study of Asthma and Allergies in Childhood (ISAAC). The overall prevalence of rhinoconjunctivitis in children aged 6 to 7 years and 13 to 14 years was 8.5 and 14.6 percent, respectively.

Efficacy

The efficacy of Ryaltris™ was evaluated in two multicenter, randomized, double-blind, placebo-and active-controlled clinical studies of 2-week duration in Study 1 (NCT02631551) and Study 2 (NCT02870205). The two studies were of similar design, including a single blind, placebo run-in period for 7 to 10 days, and enrolled a total of 2352 patients 12 years of age and older with seasonal allergic rhinitis. Patients had a history of seasonal allergic rhinitis for at least 2 years prior to screening, a positive skin prick test (wheal diameter 5mm or greater than negative diluent control) to relevant seasonal allergens (tree/grass pollen in Study 1 and ragweed/mountain cedar pollen in Study 2), and nasal symptoms defined as a 12-hour rTNSS ≥8 out of 12 and a congestion score ≥2 for the morning (AM) assessment at screening.

In Studies 1 and 2, patients were randomized to 1 of 4 treatment groups: Ryaltris™ 2 sprays (665 mcg olopatadine hydrochloride and 25 mcg mometasone furoate per spray) per nostril twice daily, olopatadine hydrochloride nasal

spray 2 sprays (665 mcg per spray) per nostril twice daily, mometasone furoate nasal spray 2 sprays (25 mcg per spray) per nostril twice daily, and vehicle placebo for 2 weeks. The olopatadine hydrochloride and mometasone furoate comparators used the same device and vehicle as Ryaltris™ but were non-US approved drugs. The demographics in Studies 1 and 2 were similar as shown in Table 1.

Table 1: Study 1 and Study 2 - Summary of Demographics

	Study 1 (N=1180)	Study 2 (N=1172)
Age		
Mean (SD)	39 (15)	40 (15)
Min, Max	12, 87	12, 82
Age Group n (%)		
12-17	115 (10)	94 (8)
Race n (%)		
White	915 (78)	956 (82)
Asian	20 (2)	22 (2)
American Indian or Alaska Native	3 (0.3)	3 (0.3)
Black or African American	230 (20)	181 (15)
Native Hawaiian or Other Pacific Islander	4 (0.3)	1 (<0.1)
Other*	8 (0.7)	9 (0.8)
Ethnicity n (%)		
Hispanic or Latino	279 (24)	329 (28)
Gender n (%)		
Female	762 (65)	737 (63)

N = number of subjects in study; n=number of subjects with data available; Min=minimum; Max=maximum; SD=standard deviation. % is based on N (total number of patients in the study)

*Other = Study 1: undefined and Study 2: White and American Indian, Multi-Racial, Mixed, African American and Caucasian, Caucasian and Hispanic, Pakistan and Caucasian.

The primary endpoint for both studies was the change from baseline in average morning (AM) and evening (PM) subject reported 12-hour reflective total nasal symptom score (rTNSS) over the 14-day treatment period. Secondary endpoints included change from baseline in average AM and PM subject-reported 12-hour instantaneous total nasal symptom score (iTNSS) over the 14-day treatment period and change from baseline in average AM and PM subject-reported 12-hour reflective total ocular symptom score (rTOSS) over the 14-day treatment period. 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 as the sum of patient's scoring of 3 individual ocular symptoms (itching/burning, tearing/watering, and redness) on a 0 to 3 categorical severity scale (0=absent, 1=mild, 2=moderate, and 3=severe). 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.

In both studies, treatment with Ryaltris™ resulted in a statistically significant improvement in rTNSS compared to olopatadine hydrochloride and to mometasone furoate as well as to placebo (except for Study 1 comparison to mometasone furoate, 95% CI -0.8-0.0). Results from both studies are shown in Table 2.

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

Treatment (2 sprays / nostril twice daily)	Study 1				Study 2			
	N	Baseline Mean	Change From Baseline LS Mean	Treatment Effect Difference LS Mean, (95% CI)	N	Baseline Mean	Change From Baseline LS Mean	Treatment Effect Difference LS Mean, (95% CI)
Ryaltris™	299	10.1	-3.5	--	291	10.1	-3.5	--
Olopatadine HCl nasal spray‡	294	10.3	-2.9	-0.6 † (-1.0, -0.2)	290	10.2	-3.1	-0.4, † (-0.8, -0.1)
Mometasone furoate nasal spray‡	294	10.2	-3.1	-0.4 (-0.8, 0.0)	293	10.2	-3.1	-0.5, † (-0.9, -0.1)
Placebo	283	10.2	-2.5	-1.0, † (-1.3, -0.6)	290	10.3	-2.4	-1.1, † (-1.5, -0.7)

* Average of AM and PM rTNSS for each day (maximum score = 12) and averaged over the 2-week treatment period.

† Statistical y significant difference ($p<0.05$) using a gatekeeping strategy.

‡ Non-US approved drugs

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.

In the two studies, Ryaltris™ also demonstrated statistically significant improvement in iTNSS as compared with placebo. Results from both studies are shown in Table 3.

Table 3: Mean Change from Baseline in Instantaneous Total Nasal Symptom Scores Over 2 Weeks* in Adults and Pediatric Patients ≥ 12 Years with Seasonal Allergic Rhinitis in Study 1 and Study 2

Treatment (2 sprays/nostril twice daily)	Study 1				Study 2			
	N	Baseline Mean	Change From Baseline LS Mean	Treatment Effect DifferenceLS Mean, (95% CI)	N	Baseline Mean	Change From BaselineLS Mean	Treatment Effect Difference LS Mean, (95% CI)
Ryaltris™	299	9.2	-3.0	--	291	9.2	-3.1	--

Olopatadine HCl nasal spray‡	294	9.4	-2.5	-0.5 (-0.9, -0.2)	290	9.4	-2.7	-0.4,† (-0.8,-0.0)
Mometasone furoate nasal spray‡	294	9.3	-2.7	-0.4 (-0.7, -0.0)	293	9.4	-2.6	-0.5,† (-0.9,0.1)
Placebo	283	9.3	-2.1	-0.9, (-1.3,0.6)	290	9.6	-2.2	-0.9,† (-1.3,0.6)

* Average of AM and PM iTNSS for each day (maximum score = 12) and averaged over the 2-week treatment period.

† Statistical y significant difference ($p<0.05$)

‡ Not commercial y 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.

Ryaltris™ demonstrated statistically significant improvement compared with placebo in the change from baseline in average morning and evening patient-reported 12-hour rTOSS (LS mean difference from placebo for Study 1: -0.5, 95% CI: -0.8, -0.2); for Study 2: -0.5, 95% CI: -0.8, -0.2) and iTOSS (LS mean difference for Study 1: -0.5, 95% CI: -0.8, -0.2); for Study 2: -0.5, 95% CI: -0.8, -0.2) over a 2-week treatment period.

Onset of action, defined as the first time point after initiation of treatment when Ryaltris™ demonstrated a statistically significant change from baseline in iTNSS compared with placebo, was assessed in both studies. Onset of action was observed within 15 minutes following the initial dose of Ryaltris™. Following the initial dose, iTNSS improved over the first week and was sustained through 2 weeks of treatment (Study 1).

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. 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 (LS mean difference from placebo for Study 1: -0.5 [-0.8, -0.3]; for Study 2: -0.5 [95% CI: -0.7, -0.2]). In these studies, the treatment differences between Ryaltris™ and the monotherapies were less than the minimum important difference of 0.5 points.

Safety

ADVERSE EVENTS

The most common adverse reactions (≥1% incidence) are dysgeusia, epistaxis, and nasal discomfort. Somnolence was reported in <1% (2 of 789) of patients treated with Ryaltris™ and no patients treated with placebo.

WARNINGS & PRECAUTIONS

Local Nasal Adverse Reactions: Epistaxis was observed in 1% of patients treated with Ryaltris™ and 0.6% of patients who received placebo in 2-week studies in patients with seasonal allergic rhinitis. Instances of nasal ulceration and nasal septal perforation have occurred in patients following the nasal application of antihistamines. 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. Localized infections of the nose and pharynx with Candida albicans have occurred from nasal administration of mometasone furoate.

Somnolence and Impaired Mental Alertness: 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. omnolence was reported in 0.3% of patients treated with Ryaltris™ and none of the patients who received placebo in 2-week studies in patients with seasonal allergic rhinitis.

Glaucoma and Cataracts: Nasal and inhaled corticosteroids including Ryaltris™ can result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

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.

Immunosuppression and Risk of Infections: Persons who are using drugs that suppress the immune system, such as corticosteroids, including Ryaltris™, 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.

Hypercorticism and Adrenal Suppression: Hypercorticism and adrenal suppression may occur when nasal corticosteroids, including Ryaltris™, are misused by taking higher-than-recommended dosages.

Effect on Growth: Nasal corticosteroids, including Ryaltris™, may cause a reduction in growth velocity when administered to pediatric patients. The safety and effectiveness of Ryaltris™ have not been established in pediatric patients less than 12 years of age and Ryaltris™ is not indicated for use in this population. Routinely monitor the growth of pediatric patients receiving Ryaltris™.

CONTRAINDICATIONS

Contraindicated in patients with known hypersensitivity to any ingredients of Ryaltris™. Hypersensitivity reactions, including wheezing, has occurred after nasal administration of mometasone furoate.

Clinical Pharmacology

MECHANISMS OF ACTION

Ryaltris™ contains both olopatadine hydrochloride and mometasone furoate. The mechanisms of action described below for the individual components apply to Ryaltris™.

Olopatadine Hydrochloride: Olopatadine is a histamine-1 (H1) receptor inhibitor. 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 activity. The precise mechanism of corticosteroid action on allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of inhibitory 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.

NEW DRUG APPROVAL

Dose & Administration

ADULTS

2 sprays per nostril twice daily.

PEDIATRICS

Children and Adolescents 12 years and older: Refer to adult dosing.

Less than 12 years: None

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Nasal spray: 665 mcg of olopatadine hydrochloride and 25 mcg of mometasone furoate in each spray.