New Medicine Recommendation

Olopatadine hydrochloride 600 micrograms / mometasone furoate monohydrate 25 micrograms per actuation nasal spray (Ryaltris®)

For the treatment of symptoms of moderate to severe seasonal and perennial allergic rhinitis

Recommendation: Black

Ryaltris® is not recommended for the relief of moderate to severe seasonal and perennial allergic rhinitis in Lancashire and South Cumbria.

Summary of supporting evidence:

- Ryaltris® provided statistically significant and clinically meaningful relief of nasal symptoms relative to the monocomponents of the spray and/or placebo in clinical trials.
- Overall, the reported common ADR are mainly local nasal reactions which could be expected to occur following the administration of a nasal spray. [1]
- Combinations of intranasal glucocorticoids and add-on oral antihistamines have demonstrated limited if any additional benefits compared to intranasal glucocorticoids alone. [2] [3] [4] [5] [6]
- Ryaltris® is cheaper than its two individual components and administration in a single formulation reduces the “washout effect” of administering two nasal spray devices sequentially and may improve concordance.
- Ryaltris® is less expensive than Dymista®, the alternative antihistamine / glucocorticoid combination nasal spray which is licensed for allergic rhinitis.
- The British Society of Allergy and Clinical Immunology advises the use of antihistamine / glucocorticoid nasal sprays (Dymista®) when symptoms remain uncontrolled on antihistamine or intranasal glucocorticoid monotherapy or a combination of oral antihistamine and intranasal glucocorticoid. [7]

Details of Review

Name of medicine (generic & brand name)**:**

Olopatadine hydrochloride and mometasone furoate monohydrate (Ryaltris®). [8]

Strength(s) and form(s):

Olopatadine hydrochloride 600 micrograms / mometasone furoate monohydrate 25 micrograms per actuation nasal spray (Ryaltris®).

Dose and administration:

Two actuations in each nostril twice daily (morning and evening).

BNF therapeutic class / mode of action:

Antihistamine and glucocorticoid (intranasal).

Licensed indication(s):

Treatment of moderate to severe nasal symptoms associated with allergic rhinitis in adults and adolescents aged 12 years and older. [8]

Proposed use (if different from, or in addition to, licensed indication above):

Patients who are refractory to first line nasal steroids or antihistamines.

Course and cost:

Ryaltris® 240 dose nasal spray cost = £13.32

Annual cost of treatment = £159.84 (assuming 12 nasal sprays would need to be supplied for 12 months treatment).

Please note that 12 months of treatment will not be necessary for some patients with allergic rhinitis.

Current standard of care/comparator therapies:

- Dymista® 120 dose nasal spray cost = £14.80

Annual cost of treatment = £177.60 (assuming 12 nasal sprays would need to be supplied for 12 months treatment).

Please note that 12 months of treatment will not be necessary for some patients with allergic rhinitis.

Combinations of intranasal steroids and oral antihistamines annual cost.

Example regimens:

- Beclometasone nasal spray combined with cetirizine tablets (approx. £33 to £183)
- Mometasone nasal spray combined with loratadine tablets (£32 to £90)
- Fluticasone propionate nasal spray combined with fexofenadine 120mg tablets (£57 to £159)

Prices obtained from the March 2022 Drug Tariff.

Costs based on number original packs of nasal spray which would need to be dispensed in a 12-month period and the dose of nasal spray required.

Relevant NICE guidance:

NICE Clinical Knowledge Summary: Allergic Rhinitis. [9]

- If there is persistent nasal itching and sneezing, options are to add in an oral antihistamine to be used regularly rather than 'as needed', or to prescribe a combination preparation containing an intranasal antihistamine (azelastine) and intranasal glucocorticoid (fluticasone propionate) such as Dymista® spray, if monotherapy with either an antihistamine or intranasal glucocorticoid is ineffective.
- The Allergic Rhinitis and its Impact on Asthma (ARIA) guideline recommends the option of combination treatment, particularly as this may act faster than intranasal glucocorticoid monotherapy, based on low- to moderate-quality evidence. It also notes that this combination is more effective for symptom reduction than the use of intranasal antihistamine monotherapy, based on low-quality evidence.
- The British Society for Allergy and Clinical Immunology guideline (BSACI) and expert consensus statement also recommend considering combination therapy second line (prescribed as Dymista® intranasal spray) if the person is more than 12 years old with moderate or severe seasonal or persistent symptoms if monotherapy with either agent is not effective. In addition, the BSACI guideline suggests concordance with treatment may be higher when the drug regimen is simple, and it found combination therapy is more effective than using either agent alone.

Background and context

Allergic rhinitis is an inflammatory disorder of the nose which occurs when the membranes lining the nose become sensitised to allergens. This triggers the release of histamine and other inflammatory mediators which act on cells, nerve endings, and blood vessels to produce sneezing, itching, nasal discharge (rhinorrhoea), and nasal obstruction. It is a common condition that affects 20% of the UK population and is increasing in incidence. The incidence of the type and severity of allergic rhinitis is related to age. Children of school age and adolescents are most commonly affected by seasonal allergic rhinitis. Adults are more likely to have perennial allergic rhinitis.

The primary goal in the management strategy of a patient with allergic rhinitis is to control their symptoms with the most acceptable treatment. Allergic rhinitis has a significant impact on a patient's quality of life and may adversely affect a patient's work, home, and social life. It is also an independent risk factor for the development of asthma, while increasing the risk of poor asthma control and exacerbation of symptoms where asthma co-exists. Treating allergic rhinitis has been associated with improved asthma control, sleep quality and exam performance. It is believed that effective management of allergic rhinitis may prevent the development of asthma. [9]

Following allergen avoidance, first-line treatment options for allergic rhinitis depend on patient symptoms/preferences and includes antihistamines (oral and intranasal) and intranasal glucocorticoids.

Ryaltris® nasal spray is an additional licensed combination spray other than Dymista® for allergic rhinitis if monotherapy with an antihistamine or glucocorticoid is inadequate. Ryaltris® was identified for review as part of the horizon scanning process undertaken by the MLCSU.

Summary of evidence

Summary of efficacy data in proposed use:

Three efficacy and safety studies were reviewed by the Swedish medicines regulatory agency and accepted for license within the EU via the mutual recognition process. [1]

Each study was randomised, double-blind, placebo-controlled, and parallel-group in design and conducted in patients 12 years of age and older with seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR) in the case of the long-term study. The two confirmatory phase III studies had a 7–10-day placebo run-in period followed by a double-blind treatment period of 15-17 days with four treatment arms that allowed comparison of Ryaltris® with each single ingredient comparator product and placebo.

The primary efficacy endpoint for the studies was the mean change from baseline in average morning and evening 12-hour reflective patient-reported Total Nasal Symptom Score (rTNSS). The rTNSS is defined as the sum of 4 nasal symptom scores: rhinorrhoea, nasal congestion, nasal itching, and sneezing (maximum score of 12) recorded twice daily in a patient diary.

Hampel et al RCT (n=1180) [10]

Over 14 days of treatment, Ryaltris® (GSP301) significantly improved average A.M. and P.M. rTNSS versus placebo (least squares mean difference -0.98 [CI95% -1.38; -0.57], $p < 0.001$) and versus olopatadine ($p = 0.003$) and approached statistical significance versus mometasone ($p = 0.059$). Ryaltris® also significantly improved average A.M. and P.M. instantaneous (i)TNSS versus placebo and both monotherapies ($p < 0.05$, all). Further, Ryaltris® significantly improved individual nasal symptoms, overall ocular symptoms (rTOSS and iTOSS), and overall quality of life versus placebo ($p < 0.01$, all). Onset of action for Ryaltris® was observed within 15 minutes

and was maintained at all subsequent time points assessed. Results for the physician-assessed nasal symptom score (PNSS) were also significant for Ryaltris® versus placebo (p < 0.001).

Treatment comparisons of average A.M. and P.M. rTNSS and iTNSS over 14 days of treatment (FAS)

Treatment Group (1 vs 2)	n1, n2	LSMD	95% CI	*p*
Average A.M. and P.M. rTNSS (primary end point)				
GSP301 vs placebo	299, 283	−0.98	−1.38 to −0.57	<0.001*
GSP301 vs olopatadine	299, 294	−0.61	−1.01 to −0.21	0.003*
GSP301 vs mometasone	299, 294	−0.39	−0.79 to 0.01	0.059
Olopatadine vs placebo	294, 283	−0.37	−0.78 to 0.04	0.076
Mometasone vs placebo	294, 283	−0.59	−1.00 to −0.19	0.004#
Average A.M. and P.M. iTNSS (secondary end point)				
GSP301 vs placebo	299, 283	−0.93	−1.28 to −0.58	<0.001*
GSP301 vs olopatadine	299, 294	−0.50	−0.85 to −0.15	0.005*
GSP301 vs mometasone	299, 294	−0.36	−0.71 to −0.01	0.041*
Olopatadine vs placebo	294, 283	−0.43	−0.78 to −0.07	0.018*
Mometasone vs placebo	294, 283	−0.57	−0.92 to −0.21	0.002*

rTNSS = reflective Total Nasal Symptom Score; iTNSS = instantaneous Total Nasal Symptom Score; FAS = full analysis set; n1 = treatment group 1; n2 = treatment group 2; LSMD = least squares mean difference; CI = confidence interval; MMRM = mixed-effect model repeated measures.
** Indicates a significant difference (p < 0.05) vs treatment group 2 by using the gatekeeping strategy.*
 # Indicates the difference was not significant per the gatekeeping strategy, even if p < 0.05.
Treatments: GSP301, olopatadine 665 μg and mometasone 25 μg; olopatadine, 665 μg; mometasone, 25 μg; placebo, GSP301 vehicle.
rTNSS and iTNSS were analyzed using an MMRM analysis with change from baseline as dependent variable, treatment group and site as fixed effect, baseline as covariate, and study day as the within-patient effect.

The percentage of patients who reported treatment emergent AEs (TEAE) was generally similar among treatments, with a greater percentage in the Ryaltris and olopatadine treatment groups than the mometasone or placebo treatment groups. Only two TEAEs, dysgeusia and headache, occurred in ≥2% of patients in any treatment group. The majority of TEAEs were mild or moderate in severity. A total of seven patients withdrew due to TEAEs, none of which was considered to be of severe intensity or a serious AE (SAE). The one SAE that occurred (spontaneous abortion in the Ryaltris group was judged to be unrelated to study treatment. No deaths occurred.

Gross et al RCT (n=1176) [11]

Ryaltris® provided statistically significant and clinically meaningful rTNSS improvements vs placebo (least squares mean difference, -1.09; CI95% -1.49; -0.69, P <0.001) and vs olopatadine (P < 0.03) and mometasone (P < 0.02). Similar significant improvements in iTNSS were also observed with Ryaltris® (P <0.05 for all). Furthermore, Ryaltris® significantly improved overall ocular symptoms, individual nasal and ocular symptoms, and quality of life vs placebo (P < 0.001 for all). Onset of action for Ryaltris® was observed within 15 minutes and was maintained at all subsequent timepoints.

Treatment Comparisons of Total Nasal Symptom Scores During 14 Days of Treatment (FAS)

Treatment Group (1 vs 2)	n 1, n 2	LSMD (95% CI)	*P* Value
Average morning and evening rTNSS (primary end point)			
GSP301 vs placebo	291, 290	−1.09 (−1.49 to −0.69)	<.001[b]
GSP301 vs olopatadine	291, 290	−0.44 (−0.84 to −0.05)	.03[b]
GSP301 vs mometasone	291, 293	−0.47 (−0.86 to −0.08)	.02[b]
Olopatadine vs placebo	290, 290	−0.64 (−1.04 to −0.25)	.001[b]
Mometasone vs placebo	293, 290	−0.62 (−1.01 to −0.22)	.002[b]
Average morning and evening iTNSS (secondary end point)			
GSP301 vs placebo	291, 290	−0.94 (−1.32 to −0.56)	<.001[b]
GSP301 vs olopatadine	291, 290	−0.41 (−0.78 to −0.03)	.04[b]
GSP301 vs mometasone	291, 293	−0.51 (−0.88 to −0.13)	.008[b]
Olopatadine vs placebo	290, 290	−0.54 (−0.92 to −0.16)	.005[b]
Mometasone vs placebo	293, 290	−0.44 (−0.81 to −0.06)	.02[b]

The mixed-effect repeated-measures analysis used change from baseline as the dependent variable, treatment group and site as the fixed effects, baseline as the covariate, and study day as the within-patient effect.
Abbreviations: FAS, full analysis set; iTNSS, instantaneous Total Nasal Symptom Score; LSMD, least squares mean difference; MMRM, mixed-effect model repeated measures; rTNSS, reflective Total Nasal Symptom Score.
[a]The GSP301 group received 665 μg of olopatadine and 25 μg of mometasone twice daily, the olopatadine group received 665 μg twice daily, and the mometasone group received 25 μg twice daily.
[b]Significant difference ($P < .05$) vs treatment group 2 using gatekeeping strategy.

Segall et al long-term study (abstract only) (n=601) [12]

In this randomised, double-blind, parallel-group study, 601 patients (ages ≥ 12 years) with PAR were randomised to twice-daily Ryaltris® (olopatadine 665 µg and mometasone 25 µg [pH 3.7]) or two vehicle formulations (placebo pH 3.7 or 7.0). The change from baseline in the average A.M. rTNSS and instantaneous TNSS, PNSS, and quality of life were assessed for Ryaltris® versus placebo ($p < 0.05$ was considered statistically significant).

At weeks 6 and 30, GSP301 provided significant and clinically meaningful improvements in average rTNSS and iTNSS versus placebo pH 3.7 ($p < 0.01$, all comparisons). Similarly, at week 52, Ryaltris® provided significant and clinically meaningful improvements in rTNSS (least-squares mean difference -0.91 [CI95% -1.35; -0.47], $p < 0.001$), and iTNSS (least-squares mean difference -0.75 [CI95% -1.17; -0.33], $p < 0.001$) versus placebo pH 3.7, with significant improvements in each individual symptom ($p < 0.05$, all comparisons). PNSS and quality of life were significantly improved versus placebo pH 3.7 at weeks 6 and 30 ($p < 0.05$, all comparisons), but these greater improvements did not reach statistical significance at week 52 (PNSS, $p = 0.552$; quality of life, $p = 0.790$).

Summary of safety data:

Safety data from RCTs is available for 3062 subjects exposed to the proposed posology and the PAR study provide long-term 52-weeks safety data for 593 subjects. In total, the safety data base includes 4672 subjects. In the included studies, dysgeusia, epistaxis and nasal discomfort have been identified as common adverse events. Findings are consistent across studies. No clinically important findings have been reported for the investigated subgroups. [1]

In the 52-week PAR study additional adverse events of upper respiratory tract infection, headache, viral upper respiratory tract infection, urinary tract infection and cough have been identified. It is noted that the difference between Ryaltris® and placebo in the PAR study is small for respiratory tract infections (6.4% vs 6.1%), viral upper respiratory tract infections (2.3% vs 2.0%) and urinary tract infections (2.3% vs 2.0%). In this study, the observed risk for infections is thus modest, although an increased risk of respiratory infections could speculatively, based on the mode of action, be related to the glucocorticoid mometasone. Overall, the reported common ADR are mainly local nasal reactions which could be expected to occur following the administration of a nasal spray. No clinically relevant changes in laboratory values have been detected in the clinical program. Serious adverse events were rare in the study population with no significant difference between groups. No deaths have been reported in the studies. [1]

The SPC for Ryaltris® contains the following list of adverse events: [8]

Frequency System Organ Class	Common (≥1/10)	Uncommon (≥1/100 to < 1/10)	Rare (≥1/1000 to < 1/100)	Not known
Infection and infestations			Bacterial vaginosis	Pharyngitis Upper respiratory tract infection
Immune system disorders				Hypersensitivity including anaphylactic reactions, angioedema, bronchospasm, and dyspnoea
Psychiatric disorders			Anxiety Depression Insomnia	
Nervous system disorder	Dysgeusia (unpleasant taste)	Dizziness Headaches Somnolence	Lethargy Migraine	
Eye disorders			Blurred vision Dry eye Eye discomfort	Cataracts Glaucoma Increased intraocular pressure
Ear and labyrinth disorder			Ear pain	
Respiratory, thoracic, and mediastinal disorders	Epistaxis Nasal discomfort	Nasal dryness	Nasal inflammation Nasal mucosal disorder Oropharyngeal pain Sneezing Throat irritation	Nasal septum perforation
Gastrointestinal disorders		Dry mouth Abdominal pain Nausea	Constipation Sore tongue	
General disorders and administration site conditions		Fatigue		
Injury, poisoning and procedural complications			Laceration	

Ryaltris® Nasal Spray is not recommended for use in children below 12 years of age as safety and efficacy has not been established in this age group.

Ryaltris® is contraindicated in patients with hypersensitivities to any of its active ingredients or excipients. Ryaltris® should not be used in the presence of untreated localised infection involving the nasal mucosa, such as herpes simplex. Because of the inhibitory effect of glucocorticoids on wound healing, patients who have experienced recent nasal surgery or trauma, or nasal septum perforation should not use a nasal glucocorticoid until healing has occurred. [8]

Strengths and limitations of the evidence:

Strengths

- Ryaltris® provided statistically significant and clinically meaningful relief of nasal symptoms relative to the monocomponents of the spray and/or placebo in clinical trials.
- Overall, the reported common ADR are mainly local nasal reactions which could be expected to occur following the administration of a nasal spray. [1]
- Combinations of intranasal glucocorticoids and add-on oral antihistamines have demonstrated limited if any additional benefits compared to intranasal glucocorticoids alone. [2] [3] [4] [5] [6]
- Ryaltris® is cheaper than its two individual components and administration in a single formulation reduces the "washout effect" of administering two nasal spray devices sequentially and may improve concordance.
- Ryaltris® is less expensive than Dymista®, the alternative antihistamine / glucocorticoid combination nasal spray which is licensed for allergic rhinitis.
- The British Society of Allergy and Clinical Immunology advises the use of Dymista® when symptoms remain uncontrolled on antihistamine or intranasal glucocorticoid monotherapy or a combination of oral antihistamine and intranasal glucocorticoid. [7]

Limitations

- No studies have directly compared Ryaltris® with either Dymista® or combinations of monotherapies of intranasal glucocorticoid and intranasal/oral antihistamines.
- In one of the confirmatory phase III studies, Ryaltris did not demonstrate a statistically significant improvement in symptoms versus mometasone monotherapy.
- Ryaltris® is more expensive than intranasal glucocorticoids combined with oral antihistamines.
- No evidence is available demonstrating efficacy in patients who have failed a combination of glucocorticoid and antihistamine.
- Evidence from the 52-week trial indicates that Ryaltris may provide short-term benefits for patients with SAR and PAR, but the benefits may not persist at 52 weeks.

Summary of evidence on cost effectiveness:

None applicable.

Prescribing and risk management issues:

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.

The Ryaltris® formulation contains benzalkonium as a preservative which may have a drying and irritant effect (also rarely hypersensitivity).

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Ryaltris® nasal spray (240-unit dose)	**2 sprays into each nostril twice daily**	**£13.32**	**£159.84**
Dymista® nasal spray (120-unit dose)	1 spray into each nostril twice daily	£14.80	£177.60

Beclometasone 50 mcg/dose nasal spray (200-unit dose)	1-8 sprays into each nostril twice daily	£3.05	£21.35 to £170.80
Fluticasone propionate 50 mcg/dose nasal spray (150-unit dose)	1-2 sprays into each nostril once or twice daily	£6.77	£33.85 to £135.40
Mometasone 50 mcg/dose nasal spray (140-unit dose)	1-4 sprays into each nostril daily	£3.87	£19.35 to £77.40
Cetirizine 10 mg tablets	One tablet daily	£0.98	£11.76
Loratadine 10 mg tablets	One tablet daily	£1.05	£12.60
Fexofenadine 120 mg tablets	One tablet daily	£1.94	£23.28
Costs based on drug tariff costs March 2022. This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:

Ryaltris® offers an alternative treatment option to Dymista® in allergic rhinitis for patients whose symptoms are not controlled by an intranasal glucocorticoid, oral antihistamine, or combination of the two.

Financial implications of the intervention:

According to Epact prescribing data for the year 2021 (January 2021 to December 2021), 1372 individual patients were identified as having received at least one prescription for Dymista® nasal spray (despite Dymista® nasal spray not being recommended in Lancashire and South Cumbria). The total spend on Dymista® nasal spray in 2021 was approximately **£66,000**. This equates to an approximate average of 3 months treatment per patient per year (consistent with treating seasonal allergic rhinitis).

If the patients currently receiving Dymista® nasal spray were switched to Ryaltris the approximate cost per annum would be **£59,400 (£6,600 cost saving).**

The approximate cost (based on average monthly cost) of treating the same number of patients with mometasone nasal spray and cetirizine tablets would be **£11,500 to £33,000** (depending on the dose).

Service Impact Issues Identified:

Provision of Ryaltris® nasal spray is not anticipated to cause any service impact issues.

Equality and Inclusion Issues Identified:

No equality/inclusion issues have been identified

Cross Border Issues Identified:

The Greater Manchester Medicines Management Group (GMMMG) does not currently have a commissioning position for Ryaltris® nasal spray.

Pan Mersey APC do not recommend the use of Ryaltris® nasal spray (indication - following inadequate symptom control using intranasal monotherapy with azelastine/glucocorticoids where the addition of the other agent is being considered). Pan Mersey APC are awaiting an application from a clinician before reviewing this commissioning position.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

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Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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