Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

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(Draft)

Olopatadine hydrochloride and mometasone furoate Nasal Spray (Ryaltris)

Indication: For the symptomatic treatment of moderate to severe seasonal allergic rhinitis (SAR) and associated ocular symptoms in adults, adolescents, and children aged 6 years and older.

Sponsor: Bausch Health, Canada Inc.

Recommendation: Do Not Reimburse

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that olopatadine hydrochloride and mometasone furoate (olopatadine-mometasone) nasal spray not be reimbursed for the symptomatic treatment of moderate to severe seasonal allergic rhinitis (SAR) and associated ocular symptoms in adults, adolescents, and children aged 6 years and older.

Rationale for the Recommendation

Although patients and clinicians identified the need for additional effective treatment options that control the symptoms of SAR, improve health-related quality of life (HRQoL), and offer better treatment tolerance and adherence, CDEC could not conclude that olopatadine-mometasone nasal spray would adequately meet the unmet needs identified based on the submitted evidence.

Two phase III, double-blind, randomized controlled trials (RCTs) (GSP301-301, and GSP301-304 [studies -301, and -304]) evaluating the efficacy and safety of olopatadine-mometasone nasal spray versus placebo and individual constituent monotherapies (i.e., olopatadine hydrochloride nasal spray and mometasone nasal spray) in adolescent and adult patients (aged 12 years and older) with moderate to severe SAR, demonstrated that, although there was a benefit compared to placebo, when compared to mometasone nasal spray, olopatadine-mometasone resulted in inconsistent statistically significant results for improvement in nasal symptoms (as measured by 12-hour reflective Total Nasal Symptom Score [rTNSS] and instantaneous Total Nasal Symptom Score [iTNSS]) and ocular symptoms (as measured by 12-hour reflective Total Ocular Scale Score [rTOSS]). Additionally, the between group differences for the results that did achieve statistical significance, were not clinically meaningful. Another phase III, double-blind RCT (GSP301-305 [study -305]) evaluating the efficacy and safety of olopatadine-mometasone nasal spray versus placebo in children (aged ≥ 6 to < 12 years) with moderate to severe SAR, demonstrated that compared to placebo, olopatadine-mometasone resulted in statistically significant improvement in nasal symptoms, but not ocular symptoms. The between group differences for the results that did achieve statistical significance were also not considered clinically meaningful. CDEC noted that there was moderate to high certainty that there was little to no difference between olopatadine-mometasone and comparators in all trials with respect to HRQoL, which was an outcome important to patients.

Though direct comparative evidence was available between olopatadine-mometasone and mometasone nasal spray from the -301 and -304 trials, there is a lack of direct comparative evidence for olopatadine-mometasone compared to other treatments for SAR. As such, comparative evidence available for this review was based on 2 sponsor-submitted network meta-analyses (NMA) which evaluated the comparative efficacy of olopatadine-mometasone versus intranasal corticosteroids, and oral antihistamines in adolescent and adult patients (aged 12 years and older), and versus intranasal corticosteroids in children (aged ≥ 6 to < 12 years). Overall, the NMAs were subject to important limitations and there was generally insufficient evidence to suggest that olopatadine-mometasone was better or worse than other established treatment options for SAR, with most estimates affected by serious imprecision. Thus, CDEC could not draw conclusions on the comparative efficacy of olopatadine-mometasone.

Discussion Points

- **Unmet Needs:** CDEC discussed multiple unmet needs identified by patients and clinicians particularly that not all patients respond to current treatments, and some patients become refractory to available treatment options. Additionally, the need for additional therapies that modify the underlying disease mechanism of SAR, as well as treatments that alleviate the symptoms of SAR while reducing unpleasant side effects (e.g., drowsiness, and stuffy or dry nose) and substantially improve HRQoL were considered. CDEC noted that compared to placebo olopatadine-mometasone nasal spray may meet some of these needs as it results in clinically meaningful improvement in nasal symptoms (measured by 12-hour rTNSS) and in ocular symptoms (measured by 12-hour rTOSS). However, CDEC was unable to ascertain whether olopatadine-mometasone nasal spray meets the unmet needs identified versus currently available active treatments. No clinically meaningful improvement in nasal symptoms, ocular symptoms, or HRQoL were observed between olopatadine-mometasone nasal spray versus mometasone nasal spray in adolescents and adults with SAR, and there was no direct comparative evidence available in children with SAR. Although there are no serious concerns with the safety profile, olopatadine-mometasone nasal spray likely results in little to no difference in the occurrence of TEAEs, compared to mometasone nasal spray, and harms or HRQoL were not evaluated in the sponsor-submitted indirect evidence. Additionally, patients and clinicians considered a need for more convenient formulations that can also improve adherence. CDEC considered the potential for improved adherence with olopatadine-mometasone due to the combination of intranasal corticosteroid and antihistamine according to the clinical experts, however, CDEC noted that there was no evidence that olopatadine-mometasone improves adherence. Overall, CDEC was unable to conclude that olopatadine-mometasone nasal spray addressed the unmet needs identified within this review.
- **Certainty of Evidence (GRADE):** CDEC discussed the GRADE certainty of evidence assessment of the clinical trials. CDEC noted that compared to placebo, olopatadine-mometasone generally resulted in an improvement in nasal and ocular symptoms with moderate to high certainty. However, the GRADE assessment concluded that there is little to no difference on the comparison between olopatadine-mometasone nasal spray versus mometasone nasal spray in nasal symptoms (moderate certainty), ocular symptoms (low certainty), HRQoL (high certainty), or TESAEs (moderate certainty). Furthermore, CDEC discussed the inconsistency in the statistical significance of the results for comparisons of olopatadine-mometasone and mometasone nasal spray, citing that the results were often not clinically meaningful.
- **Indirect Evidence:** CDEC noted that only one active comparator available in Canada (i.e., mometasone furoate nasal spray) was assessed in the clinical trial evidence for adolescents and adults (GSP301-301 and GSP301-304; olopatadine hydrochloride nasal spray was evaluated in GSP301-301 and GSP301-304 but is not available in Canada, thus, was not included in the CDA-AMC clinical report), and there are other effective treatment options available for patients with SAR. CDEC discussed the sponsor submitted NMAs comparing olopatadine-mometasone nasal spray with placebo, intranasal corticosteroids, and oral antihistamines in adolescent and adult patients (aged 12 years and older) with SAR, and compared to placebo and intranasal corticosteroids in children (aged ≥ 6 to < 12 years) with SAR. In the NMA in children, olopatadine-mometasone was favoured over intranasal corticosteroids (-0.94 points [95% CrI, -1.63 to -0.26]), but there was no difference between these treatments in the adolescent and adult NMA. There was also no difference between olopatadine-mometasone and oral antihistamines in the adolescent and adult NMA. CDEC emphasized the limitations of the NMAs, highlighting the missing relevant comparators (fluticasone furoate, bilastine, and rupatadine fumarate), and the lack of appropriate representation of relevant comparators in the drug classes, which precluded CDEC from drawing meaningful conclusions on the comparative efficacy of olopatadine-mometasone.
- **Adverse Effects:** Patients emphasized the need for reduced unpleasant side effects caused by current active treatments for SAR. Based on the evidence from clinical trials, olopatadine-mometasone nasal spray raised no new safety concerns compared to placebo or mometasone nasal spray, however, was associated with higher rates of dysgeusia, which is a known side effect of olopatadine. There were no harms evaluated in the sponsor-submitted NMAs, thus, CDEC was unable to determine the comparative safety versus other active treatments for SAR.
- **HRQoL:** CDEC noted that patients and clinicians highlighted improvement in HRQoL as an important outcome of treatment for patients with SAR. In the clinical trials, no clinically meaningful improvement in HRQoL was identified in adolescents and adults in the RQLQ (S) overall score between olopatadine-mometasone nasal spray versus mometasone nasal spray, or in children with SAR as assessed by the PRQLQ overall score between olopatadine-mometasone nasal spray versus placebo. As noted, there were no HRQoL outcomes assessed in the ITC, and the comparative effect on HRQoL of olopatadine-mometasone versus other active treatments for SAR remains unknown.
- **Generalizability:** CDEC noted that none of the three clinical trials used the term ‘moderate to severe’ to define the disease severity in the trial eligibility criteria, rather morning rTNSS and congestion scores were used to determine disease severity. However, CDEC and the clinical experts noted that disease severity generally relies on a clinician’s judgement based on the

extent to which patients are impacted by their symptoms. Furthermore, CDEC and the clinical experts consulted for this review noted that the 14-day treatment duration used in the three clinical trials might not be reflective of the duration of treatment in the real-world clinical setting, where patients are often given treatment for a longer period.

Background

Allergic rhinitis (AR), categorized as seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR), is an immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa triggered by exposure to allergens. SAR accounts for approximately 76.7% of AR cases. The estimates of prevalence of SAR in Canada range from 12.9% to 19.2% and affecting approximately 3.5 million Canadians. Patients often describe one or more of the following symptoms of AR: nasal congestion (stuffiness), nasal itching, rhinorrhea, sneezing, and cough. AR is often accompanied with allergic conjunctivitis which includes ocular symptoms such as itchiness, redness, or irritation of the eye.

According to the clinical experts, management of moderate to severe SAR involves a comprehensive approach, with the goals of alleviating symptoms, improving quality of life, and minimizing symptom exacerbations. The goals of treatment are generally consistent across age groups (i.e., adults, adolescents, and children aged 6 years and older), but the approach to treatment and consideration of medication choices may vary across these age groups. Intranasal corticosteroids alone or in combination with intranasal antihistamine are considered as first-line treatment options for moderate to severe SAR and generally preferred over oral antihistamines alone. Oral antihistamines are also used to manage itching, sneezing, and ocular symptoms, and would be considered as adjunctive therapy. Leukotriene receptor antagonists can be considered for the treatment of AR, particularly in patients who have concomitant asthma or those who do not respond adequately to other therapies. Other pharmaceutical therapies that can be used in patients with AR include ocular antihistamines, mast cell stabilizers as well as allergen immunotherapy or desensitization. Non-pharmacological management include educating patients regarding allergen avoidance measures and environmental control measures, as well as saline nasal irrigation to help alleviate nasal symptoms and reduce the need for pharmacological treatments.

Ryaltris has been approved by Health Canada for the symptomatic treatment of moderate to severe seasonal allergic rhinitis (SAR) and associated ocular symptoms in adults, adolescents, and children aged 6 years and older. Ryaltris contains both olopatadine hydrochloride and mometasone furoate, which represent histamine H1-receptor antagonist and synthetic corticosteroid, respectively. It is available as suspension for nasal spray and the dosage recommended in the product monograph is two sprays in each nostril twice daily (morning and evening) for adults and adolescents (12 years of age and older) or one spray per nostril twice daily (morning and evening) for children (6 to 11 years of age).

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 pivotal, phase III, double-blind, randomized active-controlled trials in adult and adolescent patients (12 years of age and older) with SAR (GSP301-301 and GSP301-304); 1 pivotal, phase III, double-blind, randomized placebo-controlled trial in children (6 to 11 years of age) with SAR (GSP301-305); and 2 indirect treatment comparisons
- patients' perspectives gathered by 2 patient groups, Asthma Canada and Allergy Quebec
- 2 clinical specialists with expertise diagnosing and treating patients with of SAR in adult patients or pediatric patients
- input from public drug plans that participate in the reimbursement review process
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

This review received 2 patient group input submissions from Asthma Canada and Allergy Quebec. Asthma Canada is a national charity focusing on improving the quality of life and health of people with asthma and respiratory allergies. Allergy Quebec is the main reference center in Quebec for patients with food allergies and brings together allergists, nutritionists, pharmacists, institutions and companies in the food sector. Asthma Canada collected patient input using their 2024 Annual Asthma Survey (total N = 1407 patients and caregivers, of whom 37% reported experiencing AR as a comorbidity of their asthma, and 63% reporting having had an experience of SAR). Asthma Canada also conducted two 1-on-1 interviews with patients with AR who were selected at random from the participants who completed the AR section of the survey and provided their contact information. Allergy Quebec did not perform any data collection from patients.

Both patient groups noted that AR can cause uncomfortable symptoms including runny and/or itchy nose, nasal congestion, swollen and/or itchy eyes, headaches, sinus pain and/or pressure, and tiredness, which negatively impact patients' daily activities and quality of life. In total, 82% of survey responders indicated that the physical symptoms are the most difficult and/or frustrating aspect of living with AR. Patients stated that finding a solution and/or treatment to eliminate or significantly lessen the symptoms of AR would be important for them, in particular, elimination of rhinorrhea, relief of other symptoms, and more effective medications that do not trigger asthma flare-ups. Based on the survey data from Asthma Canada, just 43% of participants reported that their current treatments can, or most of the time, control their allergic symptoms, while 57% reported that current treatments do not control their symptoms. Based on the interview results from Asthma Canada, patient concerns included the lack of efficacy or lack of sustained efficacy, and the undesired side effects (e.g., drowsiness, stuffy, or dry nose), as well as cost and accessibility problems (e.g., lack of coverage, or availability at local pharmacies) of some antihistamines.

Clinician Input

Input From Clinical Experts Consulted by The Review Team

According to the clinical experts consulted by the review team, the main goals of management of moderate to severe SAR included alleviating symptoms, improving quality of life, and minimizing symptom exacerbations. According to the clinical experts consulted by the review team, there were several unmet needs. For instance, not all patients respond adequately to currently available treatments, particularly intranasal corticosteroids and oral antihistamines. Patients can also become refractory to current treatment options over time, e.g., due to escalation of eosinophilic inflammation that would not respond to first line treatment with antihistamines. The clinical experts also noted the need for treatment options that offer better tolerability, and that can improve adherence.

According to the clinical experts consulted by the review team, olopatadine-mometasone can be used as a first-line treatment option based on individual patient needs and treatment responses, by providing a dual-action therapy combining an intranasal corticosteroid with an antihistamine. The clinical experts consulted by the review team noted that in clinical practice intranasal corticosteroids alone are usually given to patients first since they can be given once daily and may be sufficient to treat symptoms. Intranasal corticosteroids combined with antihistamines are usually reserved for when intranasal corticosteroids alone are insufficient since the combination therapy is generally more costly, requires twice daily administration, and may not be tolerated due to taste. Of note, the clinical experts consulted by the review team also noted that it is not necessary to trial monotherapy with an antihistamine or nasal corticosteroid prior to using olopatadine-mometasone.

According to the clinical experts consulted by the review team, patients most suitable or most likely to respond to olopatadine-mometasone include 1) those who are experiencing moderate to severe symptoms of SAR, those who have had inadequate response to monotherapy with intranasal corticosteroids or with antihistamines, and require both anti-inflammatory (intranasal corticosteroids) and antihistaminic/mast cell stabilizing effects to effectively manage their symptoms. 2) Patients whose quality of life is significantly impacted by SAR symptoms, affecting daily activities, sleep, and overall well-being. According to the clinical experts consulted by the review team, these patients olopatadine-mometasone would be identified via clinical evaluation and symptom assessment, and noted that assessment of symptom severity would occur through patient history and physical examination. Conversely, patients least suitable for olopatadine-mometasone include those with mild symptoms of SAR that are well-controlled

with monotherapy (either intranasal corticosteroids or antihistamines alone). The clinical experts consulted by the review team noted that allergy testing, such as skin prick tests or specific IgE testing, can identify allergens triggering symptoms but is not required specifically for initiation of olopatadine-mometasone. olopatadine-mometasone

According to the clinical experts consulted by the review team, in clinical practice, determining treatment response involves assessing various outcomes that reflect improvements in symptom control and overall quality of life. The clinical experts consulted by the review team noted that typical outcomes used include reductions in the frequency and severity of nasal and ocular symptoms such as congestion, sneezing, itching, rhinorrhea, and eye redness or watering. The clinical experts consulted by the review team noted that the extent to which these symptoms interfere with daily activities, sleep patterns, and productivity is evaluated, and assessments are conducted regularly, especially at the beginning of treatment and during peak allergy seasons, to ensure efficacy and adjust therapy as needed. According to the clinical experts consulted by the review team, the outcomes used in clinical practice are generally aligned with those in clinical trials, and include measurement of symptom scores, medication usage, and quality of life assessments. According to the clinical experts consulted by the review team, a clinically meaningful response to treatment varies according to many factors including the patient population, the severity of initial symptoms, the patient's expectations, and may even vary among physicians based on their clinical experience.

The clinical experts consulted by the review team noted several situations when discontinuation of olopatadine-mometasone should be considered, including lack of effectiveness, intolerable or persistent adverse events (AEs), or patient preference or adherence.

According to the clinical experts consulted by the review team, olopatadine-mometasone is suitable for treatment in various clinical settings, including community settings, outpatient clinics in hospitals, and specialty allergy clinics. The clinical experts consulted by the review team noted that primary care physicians can diagnose and initiate treatment for patients with SAR and monitor treatment response through regular follow-up visits and adjust therapy as needed. According to the clinical experts consulted by the review team, while specialists, such as allergists and immunologists or otolaryngologists, may offer additional expertise in managing severe or refractory cases of AR, their involvement is not always required for routine diagnosis and management with olopatadine-mometasone.

Clinician Group Input

No clinician group input was received by the review team for this review.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for Ryaltris:

- Relevant comparators
- Consideration for initiation of therapy
- Consideration for prescribing of therapy
- Generalizability
- System and economic issues

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Systematic Review

Description of Studies

Three sponsor-conducted pivotal studies, GSP301-301, GSP301-304, and GSP301-305, were included in the sponsor submitted systematic literature review (SLR). Both GSP301-301 (N = 1,176) and GSP301-304 (N = 1,180) were phase III, double-blind randomized controlled trials (RCTs) which enrolled adolescent and adult patients (aged 12 years and older) with SAR. The primary objective of GSP301-301 and GSP301-304 was to compare the efficacy of olopatadine-mometasone with placebo and individual

constituent monotherapies (i.e., olopatadine hydrochloride NS and mometasone NS) at the same dose in the same vehicle, as well as assessing the efficacy of olopatadine hydrochloride NS and mometasone NS versus placebo over 14 days of study treatment. Of note, olopatadine hydrochloride nasal spray is currently unavailable in Canada, and thereby not relevant to this reimbursement review. Results for olopatadine hydrochloride NS were not presented in the Clinical Review Report. GSP301-305 (N = 446) was a phase III, double-blind, RCT investigating children (aged ≥ 6 to < 12 years) with SAR. The primary objective of GSP301-305 was to assess the efficacy of olopatadine-mometasone relative to placebo over 14 days of study treatment. The primary endpoint of all 3 pivotal trials was patient-reported 12-hour reflective Total Nasal Symptom Score (rTNSS). Secondary efficacy and safety outcomes reported in the 3 pivotal trials included patient-reported 12-hour instantaneous Total Nasal Symptom Score (iTNSS), patient-reported 12-hour reflective Total Ocular Symptom Score (rTOSS), and harms (i.e., treatment emergent adverse events [TEAEs], treatment emergent serious adverse events [TESAEs], withdrawals, deaths). Health-related quality of life (HRQoL) outcomes evaluated in the trials included the Rhinoconjunctivitis Quality-of-Life Questionnaire Standardized Activities (RQLQ (S)) in GSP301-301 and GSP301-304, and the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) in GSP301-305.

In the GSP301-301 and GSP301-304 trials, the mean age of patients was 39.3 (standard deviation [SD] = 15.3) years and 39.6 (SD = 14.81) years, respectively. Across trials, most patients were female (64.6% and 62.9%). In the GSP301-301, the baseline rTNSS score was the same across the olopatadine-mometasone group, the mometasone NS group, and the placebo group (mean = 10.1; SD = 1.2). In GSP301-304, the baseline mean rTNSS score was 10.1 (SD = 1.2) for the olopatadine-mometasone group, 10.3 (SD = 1.3) for the mometasone NS group, and 10.3 (SD = 1.2) for the placebo group. In GSP301-305, the mean age of the study population was 8.7 (SD = 1.7) years, and there were slightly more males (56.0%) in the olopatadine-mometasone group, while in the placebo group, the proportion of male and female patients were similar (50.7% versus 49.3%). In GSP301-305, the baseline mean rTNSS score was 8.83 (SD = 1.41) for olopatadine-mometasone group and 8.84 (SD = 1.66) for the placebo group.

Efficacy Results

12-hour rTNSS over 14-day treatment period

In the full analysis set (FAS) of GSP301-301, the within-group least squares (LS) mean change from baseline in 12-hour rTNSS over the 14-day treatment period showed an improvement in all 3 treatment groups: -3.48 points (standard error [SE] = NR) in the olopatadine-mometasone group, -3.09 points (SE = NR) in the mometasone NS group, and -2.50 points (SE = NR) in the placebo group. The between-group LS mean difference in 12-hour rTNSS over the 14-day treatment period was -0.98 points (95% confidence interval [CI], -1.38 to -0.57) between the olopatadine-mometasone group and the placebo group, and -0.39 points (95% CI, -0.79 to 0.01) between the olopatadine-mometasone group and the mometasone NS group, with both point estimates of LS mean difference favouring the olopatadine-mometasone group.

In the FAS of GSP301-304, the within-group LS mean change from baseline in 12-hour rTNSS over the 14-day treatment period showed an improvement in all 3 treatment groups: -3.52 points (SE = NR) in the olopatadine-mometasone group, -3.05 points (SE = NR) in the mometasone NS group, and -2.44 points (SE = NR) in the placebo group. The between-group LS mean difference in 12-hour rTNSS over the 14-day treatment period was -1.09 points (95% CI, -1.49 to -0.69) between the olopatadine-mometasone group and the placebo group, and -0.47 points (95% CI, -0.86 to -0.08) between the olopatadine-mometasone group and the mometasone NS group, with both point estimates of LS mean difference in favour of the olopatadine-mometasone group.

In the FAS of GSP301-305, the within-group LS mean change from baseline in 12-hour rTNSS over the 14-day treatment period showed an improvement in both treatment groups: -1.6 points (SE = 0.18) in the olopatadine-mometasone group and -2.2 points (SE = 0.17) in the placebo group. The between-group LS mean difference in 12-hour rTNSS over the 14-day treatment period was -0.6 points (95% CI, -0.9 to -0.2) between the olopatadine-mometasone group and the placebo group, which favoured the olopatadine-mometasone group.

12-hour iTNSS over 14-day treatment period

In the FAS of GSP301-301, the within-group LS mean change from baseline in 12-hour iTNSS over the 14-day treatment period showed an improvement in all 3 treatment groups: -3.03 points (SE = NR) in the olopatadine-mometasone group, -2.67 points (SE = NR) in the mometasone NS group, and -2.10 points (SE = NR) in the placebo group. The between-group LS mean difference in 12-hour iTNSS over the 14-day treatment period was -0.93 points (95% CI, -1.28 to -0.58) between the olopatadine-mometasone group

and the placebo group and -0.36 points (95% CI, -0.71 to -0.01) between the olopatadine-mometasone group and the mometasone NS group, and both point estimates of LS mean difference were in favour of the olopatadine-mometasone group.

In the FAS of GSP301-304, the within-group LS mean change from baseline in 12-hour iTNSS over the 14-day treatment period showed an improvement in all 3 treatment groups: -3.11 points (SE = NR) in the olopatadine-mometasone group, -2.60 points (SE = NR) in the mometasone NS group, and -2.16 points (SE = NR) in the placebo group. The between-group LS mean difference in 12-hour iTNSS over the 14-day treatment period was -0.94 points (95% CI, -1.32 to -0.56) between the olopatadine-mometasone group and the placebo group and -0.51 points (95% CI, -0.88 to -0.13) between the olopatadine-mometasone group and the mometasone NS group, with both point estimates of LS mean difference favouring the olopatadine-mometasone group.

In the FAS of GSP301-305, the within-group LS mean change from baseline in 12-hour iTNSS over the 14-day treatment period showed an improvement in both treatment groups: -1.1 points (SE = 0.17) in the olopatadine-mometasone group and -1.8 points (SE = 0.17) in the placebo group. The between-group LS mean difference in 12-hour iTNSS over the 14-day treatment period was -0.6 points (95% CI, -1.0 to -0.3) between the olopatadine-mometasone group and the placebo group, which favoured the olopatadine-mometasone group.

12-hour rTOSS over 14-day treatment period

In the FAS of GSP301-301, the within-group LS mean change from baseline in 12-hour rTOSS over the 14-day treatment period showed an improvement in all 3 treatment groups: -2.23 points (SE = NR) in the olopatadine-mometasone group, -2.04 points (SE = NR) in the mometasone NS group, and -1.74 points (SE = NR) in the placebo group. The between-group LS mean difference in 12-hour rTOSS over the 14-day treatment period was -0.49 points (95% CI, -0.79 to -0.19) between the olopatadine-mometasone group and the placebo group and -0.19 points (95% CI, -0.49 to 0.11) between the olopatadine-mometasone group and the mometasone NS group, and both point estimates of LS mean difference were in favour of the olopatadine-mometasone group.

In the FAS of GSP301-304, the within-group LS mean change from baseline in 12-hour rTOSS over the 14-day treatment period showed an improvement in all 3 treatment groups: -2.36 points (SE = NR) in the olopatadine-mometasone group, -2.01 points (SE = NR) in the mometasone NS group, and -1.84 points (SE = NR) in the placebo group. The between-group LS mean difference in 12-hour rTOSS over the 14-day treatment period was -0.52 points (95% CI, -0.84 to -0.20) between the olopatadine-mometasone group and the placebo group and -0.35 points (-0.66 to -0.03) between the olopatadine-mometasone group and the mometasone NS group, and both point estimates of LS mean difference were in favour of the olopatadine-mometasone group.

In the FAS of GSP301-305, the within-group LS mean change from baseline in 12-hour rTOSS over the 14-day treatment period showed an improvement in both treatment groups: -0.6 points (SE = 0.13) in the olopatadine-mometasone group and -0.8 points (SE = 0.14) in the placebo group. The between-group LS mean difference in 12-hour rTOSS over the 14-day treatment period was -0.2 points (95% CI, -0.6 to 0.1) between the olopatadine-mometasone group and the placebo group, which favoured the olopatadine-mometasone group.

RQLQ (S) overall score on Day 15

In the FAS of GSP301-301, the within-group LS mean change from baseline in RQLQ (S) overall score at Day 15 showed an improvement in all 3 treatment groups: -1.54 points (SE = NR) in the olopatadine-mometasone group, -1.34 points (SE = NR) in the mometasone NS group, and -1.11 points (SE = NR) in the placebo group. The between-group LS mean difference in RQLQ (S) overall score at Day 15 was -0.43 points (95% CI, -0.64 to -0.21) between the olopatadine-mometasone group and the placebo group and -0.20 points (95% CI, -0.41 to 0.02) between the olopatadine-mometasone group and the mometasone NS group, and both point estimates of the LS mean difference were in favour of the olopatadine-mometasone group.

In the FAS of GSP301-304, the within-group LS mean change from baseline in RQLQ (S) overall score at Day 15 showed an improvement in all 3 treatment groups: -1.67 points (SE = NR) in the olopatadine-mometasone group, -1.22 points (SE = NR) in the mometasone NS group, and -1.58 points (SE = NR) in the placebo group. The between-group LS mean difference in RQLQ (S) overall score at Day 15 was -0.45 points (95% CI, -0.68 to -0.22) between the olopatadine-mometasone group and the placebo group and -0.09 points (95% CI, -0.32 to 0.14) between the olopatadine-mometasone group and the mometasone NS group, and both point estimates of the LS mean difference were in favour of the olopatadine-mometasone group.

PRQLQ overall score on Day 15

In the FAS of GSP301-305, the within-group LS mean change from baseline in PRQLQ overall score at Day 15 showed an improvement in all 3 treatment groups: -0.8 points (SE = 0.08) in the olopatadine-mometasone group and -0.5 points (SE = 0.08) in the placebo group. The between-group LS mean difference in PRQLQ overall score at Day 15 was -0.3 points (95% CI, -0.5 to -0.1) between the olopatadine-mometasone group and the placebo group, which favoured the olopatadine-mometasone group.

Harms Results

TEAEs

In the safety analysis set of GSP301-301, the proportion of patients experiencing TEAEs was 12.9% (39/302) in the olopatadine-mometasone group, which was higher than that in the mometasone NS group (7.1%, 21/294) or in the placebo group (9.4%, 27/287). The proportion of patients who had dysgeusia was 3.3% (10/302) in the olopatadine-mometasone group, 0.7% (2/287) in the placebo group, and 0 in the mometasone NS group. Headache occurred in 2.8% (8/287) of the patients in the placebo group, higher than that in the olopatadine-mometasone group (0.7%, 2/302) or that in the mometasone NS group (0.7%, 2/294). Epistaxis was reported in 1.3% (4/302) of the patients in the olopatadine-mometasone group, in 0.7% (2/294) of the patients in the mometasone NS group, and in 0.3% (1/287) of the patients in the placebo group.

In the safety analysis set of GSP301-304, the proportion of patients experiencing TEAEs was 15.6% (46/294) in the olopatadine-mometasone group, higher than that in the mometasone NS group (9.6%, 28/293) or in the placebo group (9.5%, 28/294). Dysgeusia was reported in 3.7% (11/294) of the patients in the olopatadine-mometasone group and 0 in the mometasone NS group or in the placebo group. Headache occurred in 1.4% (4/293) of the patients in the mometasone NS group, in 0.7% (2/294) of the patients in the placebo group, and 0 in the olopatadine-mometasone group. The proportion of patients who had epistaxis was 0.7% (2/294) in the olopatadine-mometasone group, 1.0% (3/293) in the mometasone NS group, and 1.0% (3/294) in the placebo group.

In the safety analysis set of GSP301-305, the proportion of patients experiencing TEAEs was 12.0% (27/225) in the olopatadine-mometasone group and 10.4% (23/221) in the placebo group. The most common TEAE in the olopatadine-mometasone group was epistaxis (2.3%, 5/225), while 0.9% (2/221) of the patients in the placebo group had epistaxis. Dysgeusia were reported in 1.3% (3/225) of the patients in the olopatadine-mometasone group and 0 in the placebo group. Headache occurred in 1.3% (3/225) of the patients in the olopatadine-mometasone group and 0.5% (1/221) of the patients in the placebo group.

TESAEs

In the safety analysis set of GSP301-301, only 1 patient had TESAE (0.3%) in GSP301-301, which was 1 spontaneous abortion in the olopatadine-mometasone group.

In the safety analysis set of GSP301-304, no patients had TESAEs occurred in the olopatadine-mometasone group. One patient (0.3%) had 1 TESAE (i.e., peritonsillar abscess) in the mometasone NS group, and 1 patient (0.3%) had 3 TESAEs (including 1 osteomyelitis, 1 syncope, and 1 foot fracture) in the placebo group.

In the safety analysis set of GSP301-305, there was only 1 TESAE (i.e., meningitis) reported in 1 patient (0.5%) in the placebo group.

Withdrawals Due to TEAEs

In the safety analysis set of GSP301-301, no patients withdrew due to TEAEs in the olopatadine-mometasone group, while 4 in the mometasone NS group and 1 in the placebo group. Reasons for withdrawal were not reported.

In the safety analysis set of GSP301-304, no patients withdrew due to TEAEs in the olopatadine-mometasone group or in the mometasone NS group. One patient (0.3%) discontinued due to foot fracture in the placebo group.

In the safety analysis set of GSP301-305, there were 4 patients (1.8%) withdrew due to TEAEs (including 1 conjunctivitis, 1 acute otitis media, 1 sinusitis, and 1 upper respiratory tract infection) in the olopatadine-mometasone group and 1 patient (0.5%) who had otitis media in the placebo group.

Mortality

No deaths were reported in the GSP301-301, GSP301-304, or GSP301-305 trials.

Critical Appraisal

The risk of bias arising from randomization process was determined to be low for all 3 pivotal trials, including GSP301-301 and GSP301-304) in adolescents and adults (aged 12 years and older) and in children (aged ≥ 6 and < 12 years old). The randomization processes were based on a computer-generated randomization scheme. Both the review team and the clinical experts consulted by the review team determined that the baseline characteristics were generally balanced across treatment groups within each of the 3 pivotal trials. The risk of performance bias due to the knowledge of treatment assignment was considered to be low by the review team as all 3 pivotal trials adopted the double-blind design, which masked the trial participants and trial personnel. An adherence rate between 75% and 125% (i.e., twice a day for 14 days to twice a day for up to 17 days) was achieved by over 90% of patients in each treatment group. The risk of bias due to missing outcome data was determined to be low for all 3 pivotal trials. Based on patient disposition information, a small proportion of patients in each treatment group of the 3 pivotal trials discontinued study for various reasons (e.g., loss to follow-up, withdrawal by patients, non-adherence). In all 3 pivotal trials, analyses in the per-protocol analysis set, which excluded patients who had non-adherence to study protocol (defined as major protocol violation), and sensitivity analyses for rTNSS, which assumed the data missing was missing not at random (MNAR) showed consistent results to those from the FAS (results not reported) according to study investigators. Definitions for patient-reported symptom scores including rTNSS (primary efficacy endpoint), iTNSS, and rTOSS were consistent across the 3 pivotal trials and considered accurate by the clinical experts consulted by the review team. However, as reflective and/or instantaneous symptom scales were primarily designed for assessment in adults, young children might need the assistance of a proxy to assess and report the severity of their symptoms. In GSP301-305, children assessed their symptoms with the assistance of their parents, guardians, or caregivers as needed. The possibility of underestimating the treatment difference between olopatadine-mometasone and placebo due to the assistance of a proxy remains unclear for GSP301-305. A gatekeeping strategy was used for rTNSS, iTNSS, and rTOSS in GSP301-301 and GSP301-304 to adjust for multiplicity; however, multiplicity was not adjusted for RQLQ(S) in these 2 trials. In GSP301-305, adjustment for multiplicity was not carried out for any outcome.

Overall, the clinical experts consulted by the review team noted that the results from the 3 sponsor-submitted pivotal trials were generalizable to the Canadian context despite some potential issues. First, the Health Canada approved indication is for patients with moderate to severe SAR. None of the 3 pivotal trials explicitly used the term ‘moderate to severe’ in the trial eligibility criteria, rather, disease severity in GSP301-301 and GSP301-304 was defined as patients with a rTNSS greater than or equal to 8 out of a possible 12 and a congestion score of 2 or more at the morning assessment at the screening visit, and as patients with a rTNSS greater than or equal to 6 out of a possible 12 and a congestion score of 2 or more at the morning assessment at the screening visit in GSP301-305. According to the clinical experts consulted by the review team, these symptom scores cut-offs correctly reflect the ‘moderate to severe’ disease severity and were appropriate in the clinical trial setting to define patients with moderate to severe SAR. However, the clinical experts consulted by the review team also noted that in the clinical setting, the cut-off symptom scores are typically not required to determine a patient’s disease severity. Instead, determination of disease severity relies on a clinician’s judgement based on the extent to which patients are impacted by their symptoms. Second, the clinical experts consulted by the review team noted that from the perspective of the real-world clinical practice, the exclusion criteria of the 3 pivotal trials were restrictive. For instance, according to the clinical experts, patients with nasal structural abnormalities and patients with a history of significant rhinitis medicamentosa were excluded from the 3 pivotal trials; while in clinical practice, these patients might still be eligible for, and benefit from olopatadine-mometasone. Despite these potential concerns, the experts consulted by the review team noted that the trial eligibility criteria were still reflective of patients they would see in the real world but may be generalized to a broader population. The clinical experts also noted that the 14-day treatment duration used in the pivotal trials might not be reflective of the duration of treatment in the real-world clinical setting, where patients are often given treatment for a longer period. Furthermore, the clinical experts highlighted that adherence to treatment in all 3 pivotal trials was higher than they would expect to see in the real-world, which may overestimate the treatment effect that would be observed in a real-world setting.

GRADE Summary of Findings and Certainty of the Evidence

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for rTNSS, iTNSS, rTOSS, RQLQ (S), and PRQLQ were set according to the presence of an important effect based on thresholds agreed upon by clinical experts consulted by the review team for this review. For harm events, the certainty of evidence was summarized narratively.

For the GRADE assessments, findings from GSP301-301 and GSP301-304 were considered together and summarized narratively per outcome and per comparison because these studies were similar in population, interventions, design, and outcome measures. The findings from GSP301-305 were assessed individually because GSP301-305 had a child population (aged ≥ 6 and < 12 years) while GSP301-301 and GSP301-304 had an adolescent and adult population (aged 12 years and older).

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Nasal symptoms: 12-hour rTNSS, 12-hour iTNSS
- Ocular symptoms: 12-hour rTOSS
- HRQoL outcomes: RQLQ (S), PRQLQ
- Harms: TESAEs

Results of GRADE Assessments

Olopatadine-mometasone Versus Placebo

Table 1 presents the GRADE summary of findings for olopatadine-mometasone versus placebo for adolescent and adult patients (aged 12 years and older) with SAR.

Table 3 presents the GRADE summary of findings for olopatadine-mometasone versus placebo for children (aged ≥ 6 year and < 12 years) with SAR.

Olopatadine-mometasone Versus Mometasone Monotherapy

Table 2 presents the GRADE summary of findings for olopatadine-mometasone versus mometasone NS for adolescent and adult patients (aged 12 years and older) with SAR.

Table 1: Summary of Findings for Olopatadine-mometasone Versus Placebo for Adolescent and Adult Patients (Aged 12 Years and Older) with SAR

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Nasal Symptoms				
12-hour rTNSS, LS mean change from baseline in average A.M. and	N = 1,163 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: -3.48 (NR)	High[a]	Olopatadine-mometasone results in a clinically important improvement in

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
P.M. 12-hour rTNSS (95% CI) Follow-up: 14 days		• Placebo: -2.50 (NR) • Difference: -0.98 (-1.38 to -0.57) GSP301-304 • Olopatadine-mometasone: -3.52 (NR) • Placebo: -2.44 (NR) • Difference: -1.09 (-1.49 to -0.69)		12-hour rTNSS over 14 days compared to placebo.
12-hour iTNSS, LS mean change from baseline in average A.M. and P.M. 12-hour iTNSS (95% CI) Follow-up: 14 days	N = 1,163 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: -3.03 (NR) • Placebo: -2.10 (NR) • Difference: -0.93 (-1.28 to -0.58) GSP301-304 • Olopatadine-mometasone: -3.11 (NR) • Placebo: -2.16 (NR) • Difference: -0.94 (-1.32 to -0.56)	High[a]	Olopatadine-mometasone results in a clinically important improvement in 12-hour iTNSS over 14 days compared to placebo.
Ocular Symptoms				
12-hour rTOSS, LS mean change from baseline in average A.M. and P.M. 12-hour rTOSS (95% CI) Follow-up: 14 days	N = 1,163 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: -2.23 (NR) • Placebo: -1.74 (NR) • Difference: -0.49 (-0.79 to -0.19) GSP301-304 • Olopatadine-mometasone: -2.36 (NR) • Placebo: -1.84 (NR) • Difference: -0.52 (-0.84 to -0.20)	Moderate[b]	Olopatadine-mometasone likely results in an improvement in 12-hour rTOSS over 14 days compared to placebo.
HRQoL				
RQLQ (S) overall score, LS mean change from baseline in in RQLQ (S) overall score on Day 15 (95% CI) Follow-up: Day 15	N = 1,140 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: -1.54 (NR) • Placebo: -1.11 (NR) • Difference: -0.43 (-0.64 to -0.21) GSP301-304 • Olopatadine-mometasone: -1.67 (NR) • Placebo: -1.58 (NR) • Difference: -0.45 (-0.68 to -0.22)	Moderate[c]	Olopatadine-mometasone likely results in little to no difference in RQLQ (S) overall score at Day 15 compared to placebo.
Harms				
TESAEs	N = 1,177 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: 3 per 1,000 • Placebo: 0 GSP301-304 • Olopatadine-mometasone: 0	Moderate[d]	Olopatadine-mometasone likely results in little to no difference in TESAEs compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Placebo: 3 per 1,000		

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] Certainty of evidence was not rated down as there were no serious concerns in risk of bias, indirectness, inconsistency, and imprecision.

[b] Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of the LS mean change from baseline in average A.M. and P.M. 12-hour rTOSS in both GSP301-301 and GSP301-304 crossed the MID, with point estimates favouring olopatadine-mometasone, despite that the point estimates were very close to the MID.

[c] Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of LS mean change from baseline in RQLQ (S) overall score in both GSP301-301 and GSP301-304 crossed the MID, with point estimates favouring olopatadine-mometasone.

[d] Imprecision was rated down for 1 level due to small number of events.

A.M. = morning; CI = confidence interval; HRQoL = health-related quality of life; iTNSS = instantaneous Total Nasal Symptom Score; MID = minimal important difference; NR = not reported; P.M. = evening; RCT = randomized controlled trial; RQLQ (S) = Rhinoconjunctivitis Quality-of-Life Questionnaire Standardized Activities; rTNSS = reflective Total Nasal Symptom Score; rTOSS = reflective Total Ocular Symptom Score; TESAE = treatment emergent adverse event.

Table 2: Summary of Findings for Olopatadine-mometasone Versus Mometasone NS for Adolescent and Adult Patients (Aged 12 Years and Older) with SAR

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Nasal Symptoms				
12-hour rTNSS, LS mean change from baseline in average A.M. and P.M. 12-hour rTNSS (95% CI) Follow-up: 14 days	N = 1,177 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: -3.48 (NR) • Mometasone NS: -3.09 (NR) • Difference: -0.39 (-0.79 to 0.01) GSP301-304 • Olopatadine-mometasone: -3.52 (NR) • Mometasone NS: -3.05 (NR) • Difference: -0.47 (-0.86 to -0.08)	Moderate[a]	Olopatadine-mometasone likely result in little to no difference in 12-hour rTNSS over 14 days compared to mometasone NS.
12-hour iTNSS, LS mean change from baseline in average A.M. and P.M. 12-hour iTNSS (95% CI) Follow-up: 14 days	N = 1,177 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: -3.03 (NR) • Mometasone NS: -2.67 (NR) • Difference: -0.36 (-0.71 to -0.01) GSP301-304 • Olopatadine-mometasone: -3.11 (NR) • Mometasone NS: -2.60 (NR) • Difference: -0.51 (-0.88 to -0.13)	Moderate[b]	Olopatadine-mometasone likely results little to no difference in 12-hour iTNSS over 14 days compared to mometasone NS.
Ocular Symptoms				
12-hour rTOSS, LS mean change from baseline in average A.M. and P.M. 12-hour rTOSS (95% CI) Follow-up: 14 days	N = 1,177 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: -2.23 (NR) • Mometasone NS: -2.04 (NR) • Difference: -0.19 (-0.49 to 0.11) GSP301-304 • Olopatadine-mometasone: -2.36 (NR) • Mometasone NS: -2.01 (NR) • Difference: -0.35 (-0.66 to -0.03)	Low[c]	Olopatadine-mometasone may result in little to no difference in 12-hour rTOSS over 14 days compared to mometasone NS.
HRQoL				
RQLQ (S) overall score, LS mean change from baseline in in RQLQ (S) overall score on Day 15 (95% CI) Follow-up: Day 15	N = 1,154 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: -1.54 (NR) • Mometasone NS: -1.34 (NR) • Difference: -0.20 (-0.41 to 0.02) GSP301-304 • Olopatadine-mometasone: -1.67 (NR) • Mometasone NS: -1.22 (NR) • Difference: -0.09 (-0.32 to 0.14)	High[d]	Olopatadine-mometasone results in little to no difference in RQLQ (S) overall score at Day 15 compared to mometasone NS.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Harms				
TESAEs	N = 1,177 (2 RCTs)	GSP301-301 • Olopatadine-mometasone: 3 per 1,000 • Mometasone NS: 0 GSP301-304 • Olopatadine-mometasone: 0 • Mometasone NS: 3 per 1,000	Moderate[e]	Olopatadine-mometasone likely result in little to no difference in TESAEs compared to mometasone NS.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of the LS mean change from baseline in average A.M. and P.M. 12-hour rTNSS in GSP301-301 and GSP301-304 included the MID, with point estimates favouring olopatadine-mometasone.

[b] Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of the LS mean change from baseline in average A.M. and P.M. 12-hour iTNSS in both GSP301-301 and GSP301-304 included the MID, with point estimates favouring olopatadine-mometasone.

[c] Inconsistency was rated down for 1 level: The point estimate of the LS mean change from baseline in average A.M. and P.M. 12-hour rTOSS was near no effect line (i.e., 0) for GSP301-301 and near the MID (i.e., 0.5) specified by the clinical experts consulted by the review team for GSP301-304. A fair proportion of the 95% CI crossed the no effect line for GSP301-301, while the 95% CI excluded the no effect line for GSP301-304. Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of the LS mean change from baseline in average A.M. and P.M. 12-hour rTOSS in GSP301-301 and GSP301-304 included the MID, with point estimates favouring olopatadine-mometasone.

[d] Certainty of evidence was not rated down as there were no serious concerns in risk of bias, indirectness, inconsistency, and imprecision.

[e] Imprecision was rated down for 1 level due to small number of events.

A.M. = morning; CI = confidence interval; HRQoL = health-related quality of life; iTNSS = instantaneous Total Nasal Symptom Score; MID = minimal important difference; NR = not reported; NS = nasal spray; P.M. = evening; RCT = randomized controlled trial; RQLQ (S) = Rhinoconjunctivitis Quality-of-Life Questionnaire Standardized Activities; rTNSS = reflective Total Nasal Symptom Score; rTOSS = reflective Total Ocular Symptom Score; TESAE = treatment emergent adverse event.

Table 3: Summary of Findings for Olopatadine-mometasone Versus Placebo for Children (Aged ≥ 6 Years and < 12 Years) with SAR

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Nasal Symptoms				
12-hour rTNSS, LS mean change from baseline in average A.M. and P.M. 12-hour rTNSS (95% CI) Follow-up: 14 days	N = 441 (1 RCT)	GSP301-305 • Olopatadine-mometasone: -1.6 (NR) • Placebo: -2.2 (NR) • Difference: -0.6 (-0.9 to -0.2)	Moderate[a]	Olopatadine-mometasone likely results in an improvement in 12-hour rTNSS over 14 days compared to placebo.
12-hour iTNSS, LS mean change from baseline in average A.M. and P.M. 12-hour iTNSS (95% CI) Follow-up: 14 days	N = 441 (1 RCT)	GSP301-305 • Olopatadine-mometasone: -1.1 (NR) • Placebo: -1.8 (NR) • Difference: -0.6 (-1.0 to -0.3)	Moderate[b]	Olopatadine-mometasone likely results in an improvement in 12-hour iTNSS over 14 days compared to placebo.
Ocular Symptoms				
12-hour rTOSS, LS mean change from baseline in average A.M. and P.M. 12-hour rTOSS (95% CI) Follow-up: 14 days	N = 441 (1 RCT)	GSP301-305 • Olopatadine-mometasone: -0.6 (NR) • Placebo: -0.8 (NR) • Difference: -0.2 (-0.6 to 0.1)	Moderate[c]	Olopatadine-mometasone likely result in little to no difference in 12-hour rTOSS over 14 days compared to placebo.
HRQoL				
PRQLQ overall score, LS mean change from baseline in in PRQLQ overall score on Day 15 (95% CI) Follow-up: Day 15	N = 441 (1 RCT)	GSP301-305 • Olopatadine-mometasone: -0.5 (NR) • Placebo: -0.8 (NR) • Difference: -0.3 (-0.5 to -0.1)	Moderate[d]	Olopatadine-mometasone likely results in little to no difference in PRQLQ overall score at Day 15 compared to placebo.
Harms				
TESAEs	N = 446 (1 RCT)	GSP301-305 • Olopatadine-mometasone: 0 • Placebo: 5 per 1,000	Moderate[e]	Olopatadine-mometasone likely results in little or no difference in TESAEs compared to placebo.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of the LS mean change from baseline in average A.M. and P.M. 12-hour rTNSS in GSP301-305 included the MID, with point estimate favouring olopatadine-mometasone and excluding MID.

[b] Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of the LS mean change from baseline in average A.M. and P.M. 12-hour iTNSS in GSP301-305 included the MID, with point estimate favouring olopatadine-mometasone and excluding MID.

[c] Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of the LS mean change from baseline in average A.M. and P.M. 12-hour rTOSS in GSP301-305 included the MID, with point estimate favouring olopatadine-mometasone.

[d] Imprecision was rated down for 1 level: According to the clinical experts consulted by the review team, a between-group difference > 0.5 points was considered clinically important (i.e., MID). The upper bound of the 95% CI of the LS mean change from baseline in PRQLQ overall score in GSP301-305 included the MID, with point estimate favouring olopatadine-mometasone.

[e] Imprecision was rated down for 1 level due to small number of events.

A.M. = morning; CI = confidence interval; HRQoL = health-related quality of life; iTNSS = instantaneous Total Nasal Symptom Score; MID = minimal important difference; NR = not reported; P.M. = evening; PRQLQ = Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; RCT = randomized controlled trial; rTNSS = reflective Total Nasal Symptom Score; rTOSS = reflective Total Ocular Symptom Score; TESAE = treatment emergent adverse event.

Long-Term Extension Studies

A long-term extension study which evaluated the long-term (52 weeks) safety, tolerability, and efficacy of olopatadine-mometasone in adults and adolescents (12 years of age and older) with PAR was submitted by the sponsor. However, given that the Health Canada approved indication is for the treatment of SAR, not PAR, the long-term study submitted by the sponsor was not considered relevant to this review and was therefore not appraised.

Indirect Comparisons

Description of Studies

The indirect treatment comparisons (ITC) submitted by the sponsor included 2 network meta-analyses (NMAs). One NMA evaluated the efficacy among olopatadine-mometasone compared to placebo, intranasal corticosteroids, and oral antihistamines in adolescent and adult patients (aged 12 years and older) with SAR. The other NMA assessed the efficacy of olopatadine-mometasone relative to placebo and intranasal corticosteroids in children (aged ≥ 6 and < 12 years) with SAR. The NMA for adolescent and adult patients was based on 13 RCTs identified from a sponsor conducted SLR, while the NMA for children was based on 4 RCTs. Efficacy was measured by 12-hour rTNSS in both NMAs.

Efficacy Results

The NMA in adolescent and adult patients (aged 12 years and older)

In the base case analysis, the mean/LS Mean difference in 12-hour rTNSS was -1.26 points (95% credible interval [CrI], -1.86 to -0.67) between the olopatadine-mometasone and placebo arms, -0.27 points (95% CrI[redacted]) between the olopatadine-mometasone and intranasal corticosteroids arms, and -0.91 points (95% CrI[redacted]) between the olopatadine-mometasone and oral antihistamines arms. Results from the sensitivity analyses were generally consistent with the results in the base case analysis.

The NMA in adolescent and child patients (aged ≥ 6 and < 12 years)

In the base case analysis, the mean/LS Mean difference in 12-hour rTNSS was -1.21 points (95% CrI, -1.86 to -0.56) between the olopatadine-mometasone and placebo arms and -0.94 points (95% CrI, -1.63 to -0.26) between the olopatadine-mometasone and intranasal corticosteroids arms. No sensitivity analyses were conducted.

Harms Results

Harms data were not examined in either NMA submitted by the sponsor.

Critical Appraisal

The 2 NMAs submitted by the sponsor defined the review questions (i.e., population, intervention, comparator, outcomes, and study design) a priori. With respect to comparators in the SLR protocol, the sponsor listed several active comparators under 2 drug classes – intranasal corticosteroids and oral antihistamines. The clinical experts consulted by the review team noted that some relevant comparators, which were approved by Health Canada for the treatment of the symptoms of SAR, were missing from the 2 classes in the protocol, including fluticasone furoate, bilastine, and rupatadine fumarate. No rationale was provided for why these comparators were not included. Consequently, missing relevant comparators from the SLR protocol might have resulted in missing evidence in the following NMAs, although the impact of this potential bias remained unknown. In addition, there is a possibility that missing comparators may jeopardize the generalizability of the NMA results to these missing comparator therapies.

To form a network, individual treatments identified from the included studies were categorized into corresponding nodes: olopatadine-mometasone, intranasal corticosteroids, oral antihistamines, and placebo. The sponsor assumed that individual drugs in the same drug class were equivalent in terms of clinical efficacy (intraclass clinical equivalency), which was considered reasonable

by the clinical experts consulted for this review. However, it was noted that within some nodes, there were only 1 or 2 individual drugs included due to lack of eligible studies which was beyond the sponsor's control. For instance, only loratadine was available and included in the oral antihistamine node in the adolescent and adult NMA. In the children NMA, the intranasal corticosteroid node only consisted of mometasone and ciclesonide. The review team determined that there was concern and associated uncertainty regarding whether only 1 or 2 individual therapies would properly represent the corresponding drug class in terms of efficacy. Thus, the interpretation of the efficacy of olopatadine-mometasone relative to the intranasal corticosteroid class and to the oral antihistamine class should be made with caution.

The clinical experts consulted by the review team generally agreed with the sponsor's evaluation and identified no serious heterogeneity arising from the patient and disease characteristics examined in the NMAs (i.e., age, gender, disease duration, baseline symptom scores, comorbidity). However, the clinical experts consulted by the review team also noted that some patient or disease characteristics which might be potential source of heterogeneity were missing from the sponsor conducted NMAs, including urban versus rural living conditions, genetic predisposition, family history of atopic diseases, and smoking or vaping status. Thus, some uncertainty concerning the results of the NMA is warranted due to these potential sources of heterogeneity, however, inclusion of these variables was beyond the sponsor's control given the limited availability of data in the included studies.

Studies Addressing Gaps in the Evidence from the Systematic Review

No studies addressing gaps in the pivotal and RCT evidence were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree
Target population	Patients aged 6 years and older, experiencing an episode of moderate to severe SAR
Treatment	Olopatadine hydrochloride and mometasone furoate nasal spray suspension (olopatadine-mometasone), daily use during an episode of SAR
Dose regimen	• Children (6 to 11 years): 1 spray in each nostril twice daily (morning and evening) • Adolescents and adults (≥ 12 years): 2 sprays in each nostril twice daily (morning and evening)
Submitted price	Olopatadine-mometasone: $56.11 per bottle (240 metered sprays)
Submitted treatment cost	Children (6 to 11 years): $0.94 per day (4 sprays) Adolescent and adults (≥12 years): $1.87 per day (8 sprays)
Comparators	• Intranasal corticosteroids[a] (INCS) • Oral antihistamines[b] (AH; included as a comparator for adolescents and adults only)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs
Time horizon	28 days
Key data sources	Efficacy of olopatadine-mometasone informed by GSP301-301 and GSP301-304 trials for adolescents and adults (compared with placebo, mometasone), and by GSP301-305 for children (compared with placebo). Efficacy of oral AH and INCS informed by sponsor-submitted network meta-analyses (NMAs).
Key limitations	• It is uncertain whether olopatadine-mometasone provides a clinical benefit relative to INCS or oral AHs for moderate to severe SAR due to limitations in the clinical evidence submitted by the sponsor. There are no head-to-head trials of olopatadine-mometasone compared to most relevant comparators. For adolescents/adults, the indirect evidence submitted by the sponsor

Component	Description
	suggests that there may be no meaningful difference in nasal symptoms between olopatadine-mometasone and oral AH or INCS. For children, the sponsor's indirect evidence suggests that olopatadine-mometasone may improve nasal symptoms compared to INCS. However, the CADTH clinical review concluded that findings of the sponsor's NMA are uncertain owing to limitations including missing comparators, the assumption that one or a few drugs properly represent drug-class efficacy, and the use of fixed-effects models in some analyses which may overestimate treatment benefit. • The sponsor's model predicts that the use of olopatadine-mometasone will lead to cost savings related to health care resource use, and that these savings will offset the acquisition cost of olopatadine-mometasone. Health care resource use was not an outcome in the olopatadine-mometasone pivotal trials, and clinical experts consulted by CADTH indicated that the frequency of health care resource use in the sponsor's model may be overestimated. If health care resource use is lower than estimated by the sponsor, the predicted savings in health care costs will be lower than estimated and olopatadine-mometasone may not offset its acquisition costs. • SAR-related ocular symptoms were not considered in the sponsor's model. SAR-related ocular symptoms are part of the Health Canada indication, and clinical expert input received by CADTH indicated that ocular symptoms are common among patients with moderate or severe SAR and can result in additional resource use. The omission of SAR-associated ocular symptoms increases uncertainty as to the incremental benefits and costs associated with the use of olopatadine-mometasone for the full Health Canada indication. • Oral AHs were not included as comparators in analysis for children. The sponsor justified this exclusion by stating that no relevant data was identified for oral AHs in the child population. However, as noted in the CADTH clinical review, the sponsor's systematic literature review protocol omitted some relevant oral AHs (i.e., bilastine, rupatadine) which are indicated for use for children. The cost-effectiveness of olopatadine-mometasone versus oral AH among children is thus unknown. • Adherence to treatment was not considered in the sponsor's model. Clinical expert input received by CADTH indicated that patients may not fully adhere to treatment in practice, for example, if they perceive no or insufficient improvement after starting treatment. If adherence is lower in clinical practice than observed in the olopatadine-mometasone pivotal trials, efficacy may be lower than included in the sponsor's model but would have no impact on drug acquisition costs. The directionality of impact on the cost-effectiveness of olopatadine-mometasone is unknown because of a lack of adherence data for comparators.
CADTH reanalysis results	• CADTH was unable to address several key limitations with the sponsor's submission, including uncertainty in the comparative clinical data and health care resource use, as well as methodological and conceptual limitations related to the model structure. These limitations prevented CADTH from deriving a base-case estimate of the cost-effectiveness of olopatadine-mometasone for the treatment of moderate to severe SAR and associated ocular symptoms. • There is insufficient clinical and economic evidence to justify a price premium for olopatadine-mometasone compared to currently available treatment options.

AH = antihistamine; ICER = incremental cost-effectiveness ratio; INCS = intranasal corticosteroid; NMA = network meta-analysis QALY= quality-adjusted life-year.
[a] In the economic model, the sponsor considered INCS to be represented by mometasone furoate, beclomethasone dipropionate, budesonide, ciclesonide, and fluticasone propionate. Costing for this group was based on the least costly generic (mometasone furoate). Efficacy for oral AH from the sponsor's NMA for children was represented by mometasone and ciclesonide, with the assumption of that efficacy would be the same for all drugs in the class.
[b] In the economic model, the sponsor considered oral AH to be represented cetirizine, desloratadine, fexofenadine, and loratadine. Costing for this group was based on the least costly generic (cetirizine). Efficacy for oral AH from the sponsor's NMA was represented by loratadine, with the assumption of that efficacy would be the same for all drugs in the class.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the modelling approach used by the sponsor introduces uncertainty that could not be resolved. Additional limitations include uncertainty in the market uptake of olopatadine-mometasone and the presence of confidential prices for comparators.

The limitations of the modelling approach to estimate the incremental budget impact could not be addressed by CADTH. Although the sponsor's base case estimates that the reimbursement of olopatadine-mometasone will be associated with incremental costs of $8,222,757 over 3 years (Year 1: $1,958,164; Year 2: $2,723,295; Year 3: $3,541,293), the impact of reimbursing olopatadine-mometasone is highly uncertain.

CDEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: November 27, 2024

Regrets:

2 expert committee members did not attend.

Conflicts of interest:

None