MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 12, 2022

SUBJECT: NDA 211746 Complete Response Resubmission Clinical Review

FROM: Xu Wang, MD, PhD
Medical Officer, DPACC/OII/OND

THROUGH: Stacy Chin, MD
Medical Team Leader, DPACC/OII/OND

THROUGH: Kelly Stone, MD, PhD
Associate Director for Therapeutic Review, DPACC/OII/OND

Executive Summary

This is a clinical review of the Complete Response resubmission of NDA 211746 for GSP 301 (proposed trade name Ryaltris) nasal spray for the treatment of symptoms of seasonal allergic rhinitis in patients 12 years and older. The original NDA, submitted on 06/28/2018, received a Complete Response on 06/20/2019 due to product quality and facility/CGMP deficiencies, but was approvable from the clinical perspective. Based on review of the clinical data submitted to the original NDA, the Applicant had adequately demonstrated substantial evidence of effectiveness and safety of GSP 301 for the proposed indication. In this NDA resubmission, the Applicant has adequately addressed the deficiencies outlined in the Complete Response letter. There are no new safety signals identified in the safety update. The NDA remains approvable from the clinical perspective.

Product Information

GSP 301 (proposed trade name Ryaltris) nasal spray (NS), is a fixed-dose combination of olopatadine hydrochloride (OLO), an H1-receptor antagonist, and mometasone furoate (MF), a corticosteroid. Each actuation delivers a 0.1 mL suspension containing 665 µg of OLO and 25 µg of MF (665 µg/25 µg). The proposed dosing regimen is 2 sprays per nostril twice daily (BID), for a total daily dose of 5,320 µg OLO and 200 µg MF. The proposed indication is "for the treatment of symptoms associated with seasonal allergic rhinitis in adult and pediatric patients 12 years of age and older (b) (4) ."

As of 01/15/2021, GSP 301 was marketed only in Australia; however, according to a press release by the Applicant in September 2021, Ryaltris has also received marketing approval in the EU, UK, and several countries in Africa, South America, and Asia. OLO and MF are approved and commercially available in the US as single

ingredient nasal spray products for SAR. OLO is available both as a branded product (Patanase) and generic. Patanase (NDA 021861) received initial U.S. approval on 04/15/2008 for the treatment of SAR in adults and children 6 years of age and older. MF is available both as a branded product (Nasonex) and generic. Nasonex (NDA 020762) received initial U.S. approval on 10/01/1997 for the treatment of SAR in adults and children 2 years of age and older.

There are currently multiple treatment modalities for symptomatic relief of SAR in the US, including nasal corticosteroids, nasal H1 receptor antagonists, oral H1 receptor antagonists and a leukotriene receptor antagonist. One other fixed dose combination nasal antihistamine and corticosteroid product (Dymista – azelastine hydrochloride and fluticasone propionate) is approved for treatment of SAR in adults and children 6 years of age and older.

Regulatory History

The Applicant originally submitted NDA 211746 for GSP 301 on 06/28/2018 as a 505(b)(2) application, relying on the Agency's prior findings of safety and effectiveness for the reference listed drugs (RLDs) olopatadine hydrochloride nasal spray (Patanase® NDA 21861) and mometasone furoate nasal spray (Nasonex® NDA 20762). Note that Nasonex® was voluntarily withdrawn from the market in May 2021 for business, rather than product quality or safety, reasons.

Based on review of the clinical data submitted to the original NDA, the Applicant had adequately demonstrated substantial evidence of effectiveness and safety of GSP 301 for the proposed indication of treatment of symptoms of SAR in patients aged 12 years and older, and therefore, the clinical team recommended Approval [see NDA 211746, Multi-Disciplinary Review and Evaluation dated 06/18/2019[1]]. However, manufacturing issues identified during the facilities' inspections and inadequate product quality data precluded approval of the application. Therefore, a Complete Response (CR) Letter was issued on 06/20/2019 and included the following deficiencies:

- During a recent inspection of the Glenmark Pharmaceuticals Ltd (FEI 3005757050) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facilities and conveyed that information to the representatives of the facilities at the close of the inspections. Satisfactory resolution of the observations is required before this NDA may be approved.
- Supporting drug master file (b) (4) has been reviewed and is currently inadequate. Deficiency comments have been forwarded to the holder of this file.
- Provide the stability results for the 30-month (25°C/60% RH) time-point for your registration batches to assure that all acceptance criteria are met all potential leachables, (b) (4), are absent or below levels of safety concern. Provide an updated extractable and leachable correlation, if applicable.
- Provide the validation data for the routine HDPE bottle extractables method and a description of the development of extractables acceptance criteria for the HDPE bottle.

[1] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804fe379&_afrRedirect=396450891665029

The CR Letter also instructed the Applicant to submit a safety update along with the Complete Response to the above deficiencies.

The Applicant filed the CR resubmission (NDA 211746, SDN 026) on 07/12/2021. The resubmission addressed the facility and product quality deficiencies outlined in the CR letter and included a clinical safety update; therefore, the resubmission was considered a complete response and adequate for review.

The CMC data, including microbiology and manufacturing information, in this CR resubmission adequately addressed deficiencies in the CR Letter. The Applicant withdrew the original manufacturing site and has proposed a new manufacturer and packager in the current submission. At the time of site assessment for the resubmission of the new manufacturer, the site profile was determined adequate. A Comparability Protocol was submitted to demonstrate the comparability of process and equipment to be used for the commercialization (b) (4). The protocol provides an update for the manufacturing (b) (4) equipment and a description of minor equipment changes, neither of which is expected to impact the drug product manufacturing (b) (4) processes as described in the NDA application. The product quality data are adequate. The CMC review team recommends Approval for this CR resubmission. For more information, refer to CMC Integrated Quality Assessment review (12/12/2021), by Craig M Bertha, PhD, and Manufacturing Addendum 1 (01/11/2022), by Ying Zhang.

Clinical Program Overview

To support the SAR indication, the Applicant conducted two adequate and well-controlled, 2-week, phase 3 pivotal trials (GSP 301-301 and GSP 301-304), along with a 2-week proof-of-concept study, a 2-week, phase 2, dose-ranging trial (GSP 301-201), and a 52-week long-term safety study (GSP 301-303). Data from these trials were submitted and reviewed in the first NDA review cycle. An overview of the efficacy and safety clinical trials is shown in Table 1.

Table 1. GSP 301 Efficacy and Safety Trials for SAR

Study ID Study Dates	Design/ Population/ Duration	Treatment Groups[a]	N	Primary Endpoint	No. of Centers/ Countries
GSP 301 Proof-of-concept Jan 2014 – Feb 2014	R, DB, DD, PG Adults with SAR for at least two years 14 days	GSP 301 665/50 µg QD GSP 301 662/25 µg BID DYMISTA 1 spray BID Patanase 2 sprays BID GSP 301 placebo BID	36 36 36 36 36	rTNSS	1 site Ontario
GSP301-201 Dec 2014 – Feb 2015	R, DB, DD, PG, PC, AC Adults with SAR for at least 2 years 14 days	GSP 301 665/50 µg QD GSP 301 665/25 µg BID GM MF 50 µg QD GM MF 25 µg BID GM OLO 665 µg BID GM OLO 665 µg QD GSP 301 placebo BID	158 159 160 159 160 158 159	rTNSS	10 sites U.S.
GSP301-301 Mar 2016 – Jul 2016	R, DB, PG, PC, AC Adults with SAR for at least 2 years 14 days	GSP 301 665/25 µg BID GM OLO 665 µg BID GM MF 25 µg BID GSP 301 placebo BID	302 297 294 287	rTNSS	37 sites U.S.
GSP301-304 Aug 2016 – Jan 2017	R, DB, PG, PC, AC Adults with SAR for at least 2 years 14 days	GSP 301 665/25 µg BID GM OLO 665 µg BID GM MF 25 µg BID GSP301 placebo BID	294 294 294 294	rTNSS	43 sites U.S.
GSP301-303 Apr 2016 – Jul 2017	R, DB, PG, PC Adults with PAR for at least 2 years 52 weeks	GSP 301 665/25 µg BID GSP 301 placebo pH 3.7 GSP 301 placebo pH 7.0	400 100 100	Safety	33 sites U.S.

[a] All treatment groups received 2 sprays/nostril
Abbreviations: R: randomized; DB: double-blind; AC: active control; PG: parallel group; PC: placebo-controlled; DD: double dummy; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; QD: once daily; BID: twice daily; GSP301: olopatadine/mometasone fixed dose combination nasal spray; GM: Glenmark; OLO: olopatadine; MF: mometasone furoate, POC: proof-of concept; rTNSS: reflective Total Nasal Symptom Score
Source: Table 14, NDA 211746 Multi-Disciplinary Review and Evaluation (6/18/2019)

In summary, the results from pivotal trials 301 and 304 provided substantial evidence of effectiveness based on statistically significant improvements in the primary endpoint, change from baseline in average AM and PM subject-reported reflective total nasal symptom score (rTNSS) over the 14-day treatment period. Comparisons were made between GSP 301, its active single components (olopatadine hydrochloride and mometasone furoate), and placebo to address the combination rule. The reductions from baseline in rTNSS were statistically significantly greater for GSP 301 compared to placebo and to the constituent monotherapies. Secondary endpoints, including instantaneous total nasal symptom score (iTNSS), reflective total ocular symptom score (rTOSS), and rhinoconjunctivitis quality of life questionnaire (RQLQ), were supportive of the primary endpoint and beneficial GSP 301 treatment effect.

The safety population consists of subjects exposed to the recommended dose of GSP 301 (2 sprays of 665 mcg OLO/ 25 mcg MF in each nostril BID) in the 4 placebo and active-controlled trials in patients with SAR of two weeks duration. The 52-week placebo-controlled, long-term safety trial in patients with perennial allergic rhinitis (PAR) provided supportive safety data. The safety profile in the GSP 301 program was consistent with the known safety of similar intranasal products in this class (i.e., antihistamines and corticosteroids). No new safety signals were identified. The overall risk-benefit assessment of GSP 301 for the treatment of SAR is favorable and supports approval from the clinical perspective.

Safety Update

In the CR resubmission, the safety update includes two new complete study reports (GSP 301-306 and GSP 301-305), a literature review, and a brief description of postmarketing experience.

Clinical Study Report for GSP 301-306

Study GSP 301-306 was conducted in Russia under the clinical trial guidelines of the Russian Authority, outside of an IND.

GSP 301-306 was a randomized, open-label, parallel group, active comparator study that evaluated the efficacy and safety of GSP 301 compared with Momate Rhino Advance nasal spray (azelastine 140 mcg and mometasone furoate 50 mcg) in 277 patients 12 years of age and older with SAR. Momate Rhino Advance nasal spray is marketed in Russia for the treatment of seasonal and perennial allergic rhinitis in patients 18 years of age and older, but is not approved in the US. Because the trial lacked blinding and an appropriate control arm, this was not considered an adequate and well-controlled trial and did not inform the overall risk/benefit assessment. Therefore, the study results were neither reviewed in detail nor incorporated into the prescribing information.

Clinical Study Report for GSP 301-305

GSP 301-305 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of GSP- 301 in pediatric subjects aged ≥6 to <12 years with SAR. Study 305 was consistent with the study design outlined in the Agreed iPSP and would have been issued as a PREA PMR had the original NDA been approved. However, the pediatric data from Study 305 was not reviewed in this resubmission due to workload constraints related to the COVID-19 pandemic and because the data is unrelated to the deficiencies of the original NDA and the indication that the Applicant is seeking at this time (i.e., treatment of symptoms of SAR in patients 12 years of age and older). The Applicant intends to submit a pediatric efficacy supplement for 6 to 11-year old patients with supporting data from study GSP 301-305 once the NDA has been approved for patients 12 years of age and older.

Literature Review

The Applicant provided findings from an updated literature search for mometasone and/or olopatadine-containing nasal sprays, covering the period from June 15, 2018 to January 15, 2021. A summary of relevant published articles is included below.

1. Wu EL, Harris WC, Babcock CM, Alexander BH , Riley CA, McCoul ED. Epistaxis risk associated with intranasal corticosteroid sprays: A systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2019;161(1):18-27.

   This is a systematic review article that included 72 clinical studies that enrolled patients ≥2 years old who were treated with intranasal corticosteroids (INCS) (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate, triamcinolone) for AR and reported epistaxis. The study showed that the overall relative risk of epistaxis was 1.48 (95% CI 1.32-1.67) for all INCS users. However, a differential effect on epistaxis among INCS agents was not clearly demonstrated. This meta-analysis confirmed an increased risk of epistaxis for patients using INCS as compared with placebo for treatment of allergic rhinitis.

   Reviewer's comment: Epistaxis is a known safety risk with INCS use.

2. Hampel FC, Pedinoff AJ, Jacobs RL, Caracta CF, Tantry SK. Olopatadine-mometasone combination nasal spray: Evaluation of efficacy and safety in patients with seasonal allergic rhinitis. Allergy Asthma Proc. 2019;40(4):261-272.

   Reviewer comment: This article reports the study results from pivotal trial GSP301-301.

3. Gross GN, Berman G, Amar NJ, Caracta CF, Tantry SK. Efficacy and safety of olopatadine-mometasone combination nasal spray for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2019;122(6):630-638.

   Reviewer's comment: This article reports the study results from pivotal trial GSP301-304.

4. Zain AM, Noh UK, Hussein S, Hamzah JC, Khialdin SM, Din NM. The relationship between long-term use of intranasal corticosteroid and intraocular pressure. J Glaucoma 2019;28(4):321-324.

   This is an observational cross-section study in a tertiary referral center of ophthalmology and otorhinolaryngology in Malaysia. A hundred (100) eyes from 50 patients on long-term intranasal steroids (>2 y) for allergic rhinitis (AR) and 90 eyes from 45 controls were included in this study. The types and dosages of the intranasal steroids were not reported in this study. The study found that prolonged use of intranasal steroids caused statistically significant increase in intraocular pressure (IOP) by a mean of 1.212 mmHg in patients with AR comparing with the controls, although no significant glaucomatous disc changes were found in AR patients. The study concluded that patients on long-term use of intranasal steroid should have a yearly eye examination to be monitored for IOP elevation and those with additional risk factors for glaucoma is closely monitored for glaucoma.

   Reviewer's comment: Increased intraocular pressure/glaucoma is a known safety risk with INCS use and described in the Warnings and Precautions for products in this drug class.

No new safety signals were identified for GSP 301 in the published literature.

Postmarketing Experience

The Applicant states that no serious adverse events have been reported to date and that all the spontaneously reported postmarketing adverse events (somnolence and off-label use) have been mild. No new safety signals for GSP 301 have been observed in the postmarket setting in Australia.

Labeling Review

No labeling negotiations occurred during the original NDA review cycle. During the NDA resubmission, the label was reviewed by the review team, labeling consultants (OPDP, DMEPA, PLT), the Division's Associate Director for Labeling (ADL) and the Agency's Labeling Policy Team (LPT). A high-level summary of significant labeling changes is provided in Table 2.

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Pediatrics

The proposed drug product triggers PREA as a new combination drug of active ingredients. The iPSP was discussed at the PeRC meeting on 12/20/2017. The PeRC agreed with the Division to grant a partial waiver of pediatric studies in children <2 years of age because studies would be impossible or highly impracticable in this age group, a partial waiver of pediatric studies in children 2 to <6 years of age because an active ingredient, olopatadine hydrochloride, would be ineffective and/or unsafe in the age group, and a deferral of the pediatric study in patients 6 to <12 years of age. The agreed-upon iPSP was received on 02/26/2018, including the planned pediatric study protocol (GSP 301-305).

A PREA PMR will be issued for the deferred pediatric study in 6 to 11 year old patients with SAR. A partial waiver of PREA requirements will be issued for studies in pediatric patients 0-5 years of age on the following grounds:

- Studies in children 0-2 years of age are impossible or highly impracticable because SAR is rarely diagnosed in this age group.
- Studies in children 2 to <6 years of age would be ineffective and/or unsafe based on the information about an active ingredient in this age group. A prior clinical study with Patanase (olopatadine hydrochloride) nasal spray in children 2 to 5 years of age failed to demonstrate efficacy and identified a safety signal of concern (nasal ulceration). Because this information must be conveyed in the label of the reference listed drug in order to use this ground for waiver, the Patanase prescribing information will need to be updated. Similar information

may be added to the Ryaltris label once language has been finalized.

Conclusion

This is an MO review of NDA 211746 GSP 301 (proposed trade name Ryaltris) nasal spray Complete Response resubmission. The Applicant has adequately addressed the deficiencies related to product quality and manufacturing facilities and the application remains approvable from the clinical perspective. Therefore, the overall recommendation is to Approve this NDA for olopatadine/mometasone nasal spray for the treatment of symptoms of SAR in patients 12 years of age and older.

CDTL Summary

I concur with Dr. Wang's assessment and recommendation to approve NDA 211746 for the fixed dose combination olopatadine/mometasone nasal spray (Ryaltris) for the treatment of symptoms of seasonal allergic rhinitis in patients 12 years of age and older.

Associate Director for Therapeutic Review Summary: Ryaltris nasal spray is a fixed-dose combination (FDC) NS of olopatadine hydrochloride (OLO), an H1-receptor antagonist, and mometasone furoate (MF), a corticosteroid. Each actuation delivers a volume of 0.1 ml suspension containing 665 µg of OLO and 25 µg of MF (665 µg/25 µg). The proposed indication is "the treatment of symptoms associated with seasonal allergic rhinitis (SAR) in patients 12 years of age and older." The proposed dosing regimen is 2 sprays per nostril twice daily (BID), for a total daily dose of 5,320 µg OLO and 200 µg MF.

Substantial evidence of effectiveness and safety was documented in the 6/18/2019 Unireview with the initial NDA submission. Review of the Safety Update included in the current Complete Response submission continues to support a favorable benefit/risk assessment. Based on these findings and the resolution of product quality and manufacturing facilities deficiencies that were identified with the initial NDA submission, I concur with Dr. Wang's assessment and recommendation for approval of NDA 211746.

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/s/

XU WANG
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STACY J CHIN
01/12/2022 02:16:20 PM

KELLY D STONE
01/12/2022 04:18:06 PM
Signing with the delegated authority of Dr. Sally Seymour, Director, DPACC