LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ryaltris

(mometasone furoate, olopatadine)

SE/H/2040/01/DC
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This module reflects the scientific discussion for the approval of Ryaltris. The procedure was finalised on 2021-04-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Glenmark Pharmaceuticals s.r.o. has applied for a marketing authorisation for Ryaltris, 600 mg/25 mcg/actuation, nasal spray, suspension. The active substance is mometasone furoate and olopatadine thus targeting different symptoms to be treated by an intranasal antihistamine and an intranasal corticosteroid.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC.

Paediatric Investigation Plan (PIP) and waiver
In accordance with article 7 of Regulation 1901/2006, as amended, the applicant has submitted a paediatric investigation plan EMEA-002514-PIP01-18. The European Medicines Agency's decision P/0170/2019 was provided on 15 May 2019. A positive opinion of the paediatric committee on full compliance with the PIP was issued on 27 March 2020 (EMA/PDCO/91300/2020).

The applicant has obtained a product-specific partial waiver from the PDCO/EMA for the age subsets 0-2 and 2-12 of the paediatric population for Ryaltris in the treatment of allergic rhinitis / rhino-conjunctivitis.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Since mometasone furoate is approved in the same concentrations and doses as a single compound, the need of studies with mometasone furoate alone is considered limited. Olopatadine HCl has not previously been approved for nasal administration in the EU but is approved in a product for ocular administration. The toxicological studies presented in the EPAR for olopatadine are considered relevant also for this application since many of the toxicity studies are performed with e.g. the oral route to increase systemic exposure. Most of the information presented are found in published literature, but sometimes the summary text from e.g. EPAR is used.

To support the FDC (GSP 301 NS), the Applicant has conducted two pharmacology studies in an ovalbumin-induced AR model to evaluate the synergy of efficacy of combination, olopatadine HCl and mometasone furoate, at two different dose ratios in male guinea pigs, a 7-day repeat dose intranasal pharmacokinetic study (GSP301-PK-003) in rats and one 13-week intranasal Good Laboratory Practices (GLP) toxicity study in rats.

III.2 Pharmacology

Olopatadine HCl is a selective, non-sedative and potent competitive histamine H1 receptor antagonist and a specific mast cell stabilizer. *Mometasone furoate* is a glucocorticoid receptor (GR) agonist with potent anti-inflammatory properties.

The pharmacological rational for combining an antihistamine and a corticosteroid is well established when anti-allergic and anti-inflammatory effects are requested.

The Applicant has conducted two exploratory pharmacology studies to evaluate the efficacy of combinations of mometasone furoate and olopatadine HCl in an allergen-induced rhinitis model in guinea pigs. Combinations of mometasone furoate with olopatadine HCl in two different ratios (10+50 µg [1:5 dose ratio] and 10+120 µg [1:12 dose ratio]) were evaluated in an ovalbumin-induced rhinitis model in male guinea pigs. Guinea pigs were sensitized intranasally with 2% ovalbumin on Days 14 - 17 and then challenged with 6% ovalbumin intranasally on Day 28. Mometasone furoate was dosed intranasally 24 hours and 1 hour before the final ovalbumin challenge, and olopatadine HCl was dosed intranasally 1 hour before the final ovalbumin challenge. The combination of mometasone furoate and olopatadine HCl was administered intranasally 1 hour before the final ovalbumin challenge on Day 28. Treatment with olopatadine HCl primarily inhibited the sneezing response, which was expected for an antihistamine. Treatment with mometasone furoate primarily inhibited nasal inflammation and nasal eosinophilia, which was expected for a corticosteroid. In both studies, the combination of mometasone furoate and olopatadine HCl had a synergistic effect on ameliorating rhinitis. Significant inhibition of the sneezing response and allergen-induced nasal inflammation was observed in the combination arms and the effect was greater than in the respective monotherapy arms.
There was no discussion on the possible mechanism behind this observed synergistic effect. The potential for pharmacodynamic interactions between the two substances in the FDC is included in the LoQ in the clinical section.
The secondary pharmacodynamics of olopatadine HCl was only briefly presented. The applicant claims that olopatadine HCl showed no significant interaction with other physiologically relevant receptors, it is however not described which these physiologically relevant receptors are. Olopatadine was also described to be devoid of any significant activity on cyclooxygenase and 5-lipoxygenase enzymes. No data on potential secondary pharmacodynamic effects of mometasone furoate or the combination have been presented.

Intra-nasal administration is explored as a route to deliver compounds to the brain. Although this is not the goal with olopatadine or mometasone, there is a potential delivery to the CNS which means that other receptors could be considered physiologically relevant than when other routes of administration have been used.

Toxicity and safety pharmacology studies have however been studied with high systemic exposures and no indications of CNS-effects have been observed. Furthermore, considering the clinical experience with the compounds, the lack of secondary pharmacology studies addressing this potential issue is considered acceptable.

Several studies are published investigating the safety pharmacological properties of olopatadine. The CNS studies indicated that the potential CNS effects after olopatadine treatment will be minimal.

A significant QTc prolongation was observed in dogs administered 100 mg/kg olopatadine orally. The systemic exposure after this dose is not presented. In the ocular product, it is stated that the potential risk of torsade de pointes caused by olopatadine would only be at dosages largely exceeding what will be used clinically. The clinical ocular dose in Opatanol is 0.2 mg/day, the intended nasal dose 4.8 mg/day. The nasal route of administration will result in a higher systemic exposure than the ocular route. The 100 mg/kg dose in dogs corresponds to 2000 mg/m2 based on body surface area. The human daily nasal dose is 4.8 mg/day. Assuming a 60 kg person this dose, based on body surface area, would be (4.8/60)*37 = 2.96 mg/m2, which is >600 times lower than the dose associated with QTc prolongation in dogs. Taken together, the conclusion that the QTc prolongation effect in dogs occurs at dosages exceeding the clinical dosages is agreed upon. QT interval was measured in the clinical Phase 3 studies, see clinical section.

No safety pharmacology data for mometasone furoate has been presented. However, considering the low systemic exposure and the clinical experience with the compound, this is considered acceptable.

In summary, the pharmacodynamics presented for olopatadine HCl and mometasone is considered sufficient for the present indication and intended use of the product.

III.3 Pharmacokinetics

The pharmacokinetics of olopatadine and mometasone has been described. The Applicant has conducted a 7 days pharmacokinetic study with intra nasal administration in rat with the combination and with olopatadine and mometasone separately. Systemic exposure of mometasone was not detected (below level of quantification). Absorption of olopatadine to the systemic circulation was quick from the nasal administration. Systemic exposure of olopatadine was higher in female vs male rats, both Cmax and AUC were approximately 2 times higher. The exposure of olopatadine in combination with mometasone appeared to be higher than when olopatadine was administered as a single agent in rat but not in human.

No analysis method was developed to support the 3-months GLP toxicity study in rats, and no samples to quantify either olopatadine or mometasone were collected. This is considered a weakness, but is acceptable since no signs of systemic toxicity was observed in the toxicity study and the clinical experience of both the compounds.

In the already approved product with olopatadine, Opatanol, the daily dose is one drop in the affected eye(s) twice daily. The concentration of olopatadine is 1 mg/mL. Measured plasma concentrations after ocular administration of Opatanol is ranging from below the assay quantitation limit (<0.5 ng/mL) up to 1.3 ng/mL. For the nasal administration the Applicant has shown a Cmax of 20 ng/mL.

Distribution of ^{14}C-olopatadine after an oral dose was mainly to organs involved in metabolism and excretion with highest distribution was noted in secretory organs. Very low radioactivity was observed in the brain. It is not known if the nasal route could increase the exposure in the brain.

In a 21-day study in rats, an increase in radioactivity concentration was seen due to repeated administration, with a steady state being reached between the 7th and 14th dose. Whereas the $t_{1/2}$ of plasma radioactivity after the single dose administration was about 16 hours, the $t_{1/2}$ in the repeated dose 21-day study was 41 hours. In a study were olopatadine was administered intravenous to rats the

reported $t_{1/2}$ was 4.55 hours, indicating that the radioactivity included also metabolites.

In humans several metabolites have been detected, however no major metabolite. According to the product information of the ocular product, similar metabolites were demonstrated in human as in rats and dogs.

No data was provided for mometasone. This is considered acceptable considering the very limited systemic exposure and clinical experience with mometasone and nasal administration.

III.4 Toxicology

A toxicology programme based on published studies and a 3-months repeat dose toxicity study with the combination have been presented. Since mometasone furoate is approved in the same concentrations and doses as a single compound, the need of studies with mometasone furoate alone is considered limited. Olopatadine HCl has not previously been approved for nasal administration in the EU but is approved in a product for ocular administration. The toxicological studies presented in the EPAR for olopatadine are considered relevant also for this application since many of the toxicity studies are performed with e.g. the oral route to increase systemic exposure.

Single-dose toxicology studies for olopatadine have been presented by the applicant. Single dose toxicity studies are considered of limited relevance for the present application. Studies were conducted in mice, rats, and dogs via oral and iv routes. The doses used were of limited value for the present application.

The Applicant conducted a 3-months nasal repeat dose toxicity study in rats. In the study the combination of olopatadine HCl and mometasone furoate was investigated in parallel to the single agents. There were no test article-related clinical signs or changes in food consumption, ophthalmic examinations, haematology parameters, coagulation parameters, clinical chemistry parameters, or macroscopic urinalysis data during this study. There were no test article-related gross observations, changes in absolute or relative organ weights, or microscopic findings observed at study termination. The dosing was in other words well tolerated. No nasal irritancy was observed. Two animals died during the study with no clear cause of death established. It is however reasonable that the observed haemorrhage represents the large volume of the administered dose rather than a direct toxic effect of the test article. The systemic exposure of olopatadine HCl and mometasone furoate was not measured in the 13-week toxicity study. The proposed NOAEL of the formulation to be marketed was the highest dose tested, that is olopatadine HCl 1064 µg/day and mometasone furoate 40 µg/day. The margin to the clinical maximum recommended dose was calculated both on nasal surface area, body weight and body surface area. With the nasal surface area, the dose at NOAEL was 2.3 times the clinical dose, using the body surface area, the NOAEL was at a dosage 8-fold the maximum daily human dose. In the pharmacokinetic study, systemic exposure of olopatadine was measured after 7 days nasal administration. The measured C_{max} was 13-fold the observed human C_{max}. AUC24 hr was 3.3 times above the human AUC. C_{max} and AUC in the rat study were higher in female rats, the values used here are from the male rats.

Olopatadine is not considered mutagenic. No mutagenic effects are expected at therapeutically relevant doses of mometasone furoate.

Carcinogenicity studies have previously been conducted for olopatadine (mice and rats, oral administration), and mometasone furoate (mice and rats via inhalation). Olopatadine and mometasone furoate are not considered to have a carcinogenic potential.

The applicant has described the reproductive studies that are the basis of the current labelling for olopatadine and mometasone furoate. It is agreed that no reproductive and development toxicity study with the combination needs to be conducted.

The effects of olopatadine HCl on fertility were investigated in rats with doses up to 400 mg/kg

administered orally. Decrease in fertility index and reduced implantation rate were observed at doses 732-fold the maximum recommended human nasal dose based on body surface. No effects were seen at a dose 91-fold the human nasal dose.

Olopatadine caused an increase in the post implantation loss at ≥60 mg/kg/day in rats, corresponding to 110-fold the human nasal dose based on body surface. A reduced number, although not statistically significant, of alive foetuses in rabbits were also observed at ≥25 mg/kg/day corresponding 91-fold the human nasal dose based on body surface. Adverse effects on the pups (e.g. low birth weight) were also shown at high oral doses, which were associated with maternal toxicity. No teratogenic potential was shown in rats at 600 mg/kg and in rabbits at 400 mg/kg.

Several Segment III studies were conducted to elucidate the findings of low body weight and delayed development observed. It was demonstrated in lactation studies that the effects were likely due to secretion of the olopatadine in the milk and subsequent dosing of the pups.

The SmPC 4.6. advice for women of child-bearing potential is as follows:

...should not be used in pregnancy unless the potential benefit to the mother justifies any potential risk to the mother, foetus or infant.

III.5 Ecotoxicity/environmental risk assessment

Mometasone furoate: The mometason furoate (MOM) ERA dossier provides a Phase I predicted environmental concentration estimate for surface waters (PECsw) of 0.001ug/L (default calculation using a maximum dose of 200ug and a Fpen of 0.01). MOM has a primary biodegradation half-life of 31d in activate sludge and that it is not readily biodegradable. The MOM Koc of soils was between 36640 and 10592L/kg while a sludge Koc was 5255L/kg (<10 000L/kg), indicating that the substance is not distributed to land via sewage sludge. It is very persistent in sediments with a DT50 of 172-223d (12C temperature adjusted value) and with a strong dissipation from the water layer to sediment.

In the aquatic toxicity assessment, the most sensitive species class was fish (*Pimephales promelas* in a FELS study), giving a NOEC of 0.00014mg/L and a LOEC of 0.00022mg/L. Chronic exposure to *Daphnia magna* gave a NOEC of 0.34mg/L (max concentration in test, LOEC > 0.34mg/L) while green algae had an NOEC of 3.2mg/L (LOEC > 3.2mg/L). There were no indications of acute toxicity (3h) among activated sludge microorganisms (NOEC 1000mg/L). Exposure of sediment-dwellers (*Chironomus riparius*) gave a NOEC (adjusted for 10% organic content) of 45mg/kg. A bioconcentration assessment in Bluegill sunfish gave a kinetic BCF of 104.9-107.1L/kg, indicating low potential for bioaccumulation. Based on the use of the Phase I PECsw, the risk quotients for all compartments mediums were RQ < 1.0 (and RQ < 0.1 for microorganisms). The highest RQ (0.071x) was for surface water using the FELS data.

Remaining issues are a missing OECD TG234 (characterizing MOM endocrine disruption potential on sexual development in fish) which the applicant has committed to provide before Q4 2023 (in the form of a Letter of Access). With regard to PBT assessment, MOM is positive for P and T but not B and is therefore not considered a PBT or vPvB candidate. Before the remaining concern is resolved, the ERA and the conclusion about environmental risk cannot be finalized.

Olopatadine hydrochloride: The provided olopatadine hydrochloride (OLP) ERA dossier gives a Phase I PECsw of 0.024ug/L (default calculation using a maximum dose of 4800ug and a Fpen of 0.01), triggering a Phase IIA assessment. OLP has a log Kow of 0.317 at pH 7 and is not considered a PBT candidate. OLP is not readily biodegradable. An OECD TG121 HPLC-based test provided a preliminary Koc of 145. While the OECD TG121 value is insufficient for Phase IIB risk assessment calculations, it is sufficient to argue that OLP is unlikely to be distributed to land via sewage sludge and that a terrestrial risk assessment is not necessary.

In the aquatic toxicity assessment, there was some uncertainty regarding the FELS study. The applicant proposes a max-concentration NOEC (10.3mg/L) despite there being a statistically significant reduction (9-12%) in fish size at all concentrations (minimum concentration/LOEC = 1.26mg/L) on the basis that the extent of the effect is small and that there is no clear concentration response profile. This argument is not accepted as 1) all three concentrations demonstrated statistical significance, 2) the so absence of a clear monotonic concentration-response curve may be due to the limited concentration range tested (i.e. only from 1.26 to 10.3mg/L), 3) the overall data had acceptable quality for the used statistical approach (assessed by Shapiro-Wilk's and Levene's test, with outliers removed), 4) no strong support for the proposed NOEC can be drawn from the range finding study as it used a shorter exposure duration (20d vs 33d). No NOEC can therefore be determined (i.e. NOEC <1.26mg/L and LOEC 1.26mg/L), making fish the most sensitive species class. That being said, while formally, a new FELS study would normally be required, it is agreed that the effect is small and it is also very unlikely that a new FELS study would provide a new NOEC that would be >1000x more sensitive compared to the present NOEC (required to trigger an environmental risk re-classification for surface water based on use of the Phase I PECsw). The second most sensitive model organism class is green algae with a NOEC of 7.97mg/L followed by *Daphnia magna* with a NOEC of 10mg/L (LOEC > 10mg/L). There was an indication of a limited acute toxicity effect on active sludge microorganisms with 9% respiration inhibition at 1000mg/L. Based on the use of the Phase I PECsw, the risk quotients for all compartments mediums were RQ < 1.0 (and RQ < 0.1 for microorganisms). The highest RQ (0.00019x) was for surface water using the Phase I PECsw value and the FELS data with a <NOEC/LOEC value of 1.26mg/L.

Overall, OLP is not an PBT candidate and based on the RQ estimates, very unlikely to be an environmental risk. That being said, there are several remaining uncertainties that need to be resolved before the OLP ERA can be finalized. There is a commitment to submit an OECD TG106, OECD TG308 and sediment-dweller toxicity study (OECD TG218) before Q4 2023.

Conclusions on ERA studies: The active substances (MOM, OLP) are not PBT candidates but a final environmental risk assessment cannot be finalized until the various concerns have been resolved. The applicant is committed to providing missing studies and an updated ERA before Q4 2023.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ryaltris (GSP 301 NS) is a new fixed-dose combination product intended for local administration and local action; thus, pharmacokinetic data is mainly related to safety and not to efficacy. The systemic exposure from the FDC has been compared to that of the monocomponents in order to assess pharmacokinetic drug interactions and in order to establish a bridge to the monotherapy products. The monotherapy product for olopatadine is however not approved in the EU as a nasal spray, only as eye drops. However, there is sufficient safety data with the fixed dose combination; thus, the PK bridge to the monocomponents is not necessary for establishment of systemic safety but is needed in order to bridge to general PK data with the monocomponents.

IV.2 Pharmacokinetics

Pharmacokinetics of olopatadine and mometasone furoate when administered together as FDC GSP301-1 NS or GSP 301 NS and as the respective monotherapies was evaluated in three studies: two phase 1 single dose relative bioavailability studies in healthy subjects (GSP 301-101 and GSP 301-102) and a phase 3 study (GSP 301-301) in subjects with SAR.

Bioanalytical methods

Adequately validated methods were used for the bioanalysis of olopatadine and mometasone furoate in human plasma.

Population pharmacokinetic analysis

The applicant has performed a population PK (popPK) analysis based on PK data of olopatadine and mometasone furoate from the phase 1 and phase 3 studies, GSP 301-101, GSP 301-102 and GSP 301-30. Only data from FDC formulation, GSP301 NS, was used in the analysis. The analyses were performed using the nonlinear mixed effects modelling.

The final popPK model, for both mometasone and olopatadine, was a two-compartment model with first order absorption and lag time. Clearances and volumes of distributions were allometrically scaled by body weight using the power model and exponents of 0.75 for clearances and 1 for volumes of distribution (based on prior knowledge and mechanistic reason). Race, age, ethnicity and sex were not identified as significant covariates on clearance. PopPK parameter estimates are shown in Table 1 and Table 2.

Table 1: Final estimates of popPK Model for Olopatadine

Parameters	Description	Estimates (RSE%)	Estimates Bootstrap Median (95% CI)	Variance (RSE%)	Variance Bootstrap Median (95% CI)	Between-subject variability (%CV)
KA	First order absorption rate constant (hr^{-1})	2.50 (0.007)	2.500 (1.978-3.367)	0.833 (33)	0.655 (0.312-1.104)	91
CL	Clearance (L/hr)	28.1 (6)	27.9 (25.1-30.8)	0.426 (12)	0.372 (0.247-0.465)	65
V2	Central volume of distribution (L)	105 (7)	105 (93-130)	0.173 (13)	0.178 (0.081-0.433)	42
V3	Peripheral volume of distribution (L)	325 (32)	323 (137-550)	0.237 (183)	0.190 (0.0000237-0.523)	49
Q	Inter-compartmental clearance (L/hr)	6.43 (5)	6.34 (4.80-7.78)	0.245 (60)	0.245 (0.138-0.378)	50
ALAG1	Absorption lag time (hr)	0.061 (16)	0.057 (0.048-0.061)	0.192 (54)	0.059 (0.014-0.191)	44
ADD	Additive error	0.053 (14)	0.053 (0.029-0.068)			
PROP	Proportional error	0.161 (3)	0.162 (0.139 – 0.187)			
TH9	Covariate effect for Study on ADD	9.53 (15)	9.50 (1.21-20.3)			
TH10	Covariate effect for Study on PROP	2.33 (4)	2.34 (1.98 – 2.88)			

Source: Table 5 in report GSP 301 NS – Population PK

Table 2: Final estimates of popPK model for mometasone furoate

Parameters	Description	Estimates (RSE%)	Estimates Bootstrap Median (95% CI)	Variance (RSE%)	Variance Bootstrap Median (95% CI)	Between-subject variability (%CV)
KA	First order absorption rate constant (hr^{-1})	0.588 (7)	0.589 (0.527-0.676)	0.057 (42)	0.056 (0.000279-0.112)	24
CL	Clearance (kL/hr)	1.87 (4)	1.87 (1.72-2.03)	0.328 (10)	0.322 (0.258-0.395)	57
V2	Central volume of distribution (kL)	3.54 (16)	3.52 (2.81-4.48)	0.413 (34)	0.411 (0.232-0.618)	64
V3	Peripheral volume of distribution (kL)	47.7 (18)	47.5 (37.6-60.7)	0.691 (33)	0.656 (0.405-0.954)	83
Q	Inter-compartmental clearance (kL/hr)	4.49 (14)	4.48 (3.74-5.40)	0.404 (29)	0.396 (0.208-0.589)	64
ALAG1	Absorption lag time (hr)	0.080 (14)	0.080 (0.080-0.103)	0.236 (50)	0.229 (0.117-0.323)	49
ADD	Additive error	0.104 (14)	0.105 (0.054-0.218)			
PROP	Proportional error	0.113 (5)	0.112 (0.089-0.135)			
TH9	Covariate effect for Study on ADD	1.602 (18)	1.480 (0.017-3.142)			
TH10	Covariate effect for Study on PROP	2.693 (5)	2.757 (2.169-3.551)			

Source: Table 4 in report GSP 301 NS – Population PK

Visual predictive checks (VPC) plots from study 301-301 are shown in Figure 1.

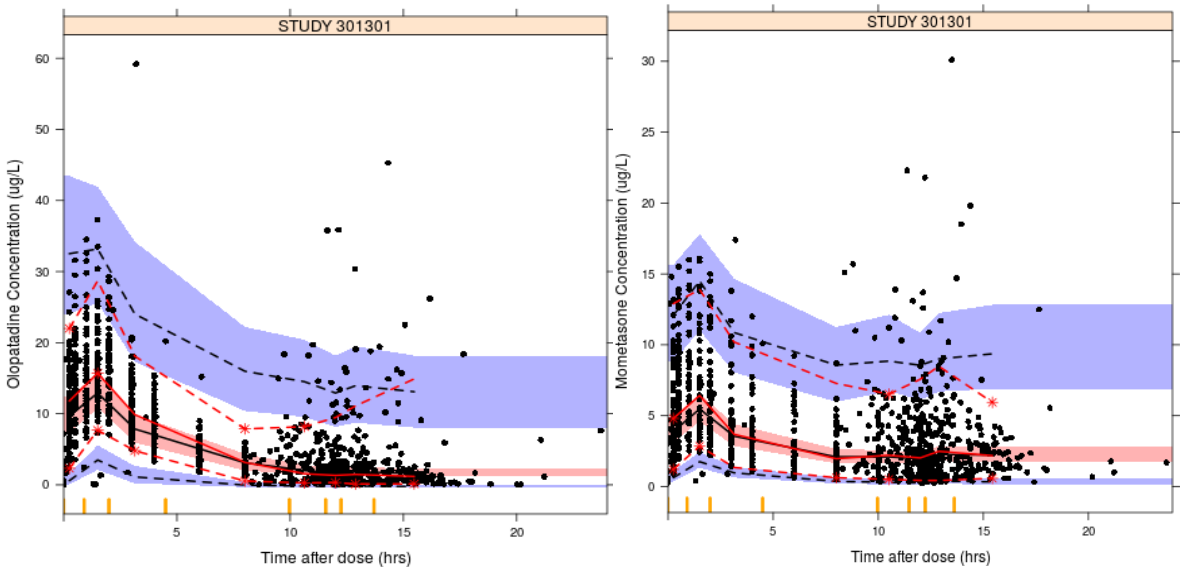

Figure 1: VPC plots of olopatadine and mometasone furoate up to 24 hours after dosing, in study 301-301

Red solid line represents median of observed data, black solid line represents median of predicted data, red broken lines represent 90% intervals of observed data, black broken lines represent 90% prediction intervals of predicted data and shaded area presents 95% CI of the prediction intervals. Black circles represent observed data.

The model diagnostics indicated that there were issues with the stability of the popPK models. In addition, the models could not describe the C_{max} of mometasone and olopatadine. Due to the issues

identified, the results of the popPK analysis, including covariates analysis should be interpreted with caution.

Bioavailability
Studies GSP-301-101 and -102 were randomized, single-centre, single-dose, open-label, three-period, six-sequence, cross-over studies in adult healthy volunteers to assess the relative bioavailability of olopatadine or mometasone furoate given as the FDC compared to the US marketed products Patanase (olopatadine) or Nasonex (mometasone furoate), or Glenmark's monocomponent product in the same formulation as the FDC, respectively. A single administration of 2 sprays in each nostril for a total of 4 sprays was administered to each subject after an over-night fast. Each spray delivered 665 µg of olopatadine HCl and 50 µg of mometasone furoate for the FDC product, or the corresponding dose of the monocomponent. These studies were not performed with the to-be-marketed formulation, but with the previous formulation (GSP301-1 NS), which was identical to the marketing formulation, with the exception of the concentration of mometasone furoate.

Comparisons were made to a product that is approved in the USA (Patanase nasal spray), and not the EU approved eye drops Opatanol. Also regarding Nasonex, the product used was sourced in the US. As this is a complete application, and this study aims at bridging to the literature for special populations and interactions, this may be acceptable if further original literature is provided to support the claims in the SmPC. Acceptable literature was provided to support the claims for both olopatadine and mometasone furoate.

The results of both studies are summarised in Table 3. According to the EU bioequivalence guideline, AUC_{0-t} and C_{max} are the primary parameters for immediate release formulations; thus, this assessment focuses on these parameters.

For olopatadine, strict BE criteria were fulfilled only between the two olopatadine monocomponents, while the FDC had lower olopatadine C_{max} and AUC_{0-t} than each monocomponent product. The olopatadine exposure is nevertheless considered similar compared to the monocomponent products, thus not indicating a significant effect of mometasone furoate on olopatadine pharmacokinetics.

AUC_{0-t} of mometasone furoate was similar for the FDC compared to (US-sourced) Nasonex, while C_{max} was 42% higher. However, considering that the to-be-marketed product will be administered as 100 µg BID instead of 200 µg QD, the recommended dose of the FDC is not likely to give a higher mometason C_{max} compared to Nasonex. For the FDC compared to Glenmark mometasone furoate NS, AUC_{0-t} and C_{max} was comparable, thus not indicating a significant effect of olopatadine on mometason furoate pharmacokinetics. Also, the comparison between the two monocomponent products resulted in similar AUC_{0-t} and C_{max}.

Table 3: Relative bioavailability of olopatadine and mometasone furoate with different formulations

	C_{max}		AUC_t		AUC_∞	
Study GSP 301-101	N	GMR (90% CI)	N	GMR (90% CI)	N	GMR (90% CI)
GSP 301-1 NS vs Olopatadine HCl NS QD (olopatadine in GSP 301 NS vehicle)	28	86.63 (75.70 - 99.15)	28	86.92 (75.21, 100.47)	24	92.83 (81.23 - 106.09)
GSP 301-1 NS vs PATANASE	29	84.68 (69.96 - 102.49)	29	87.87 (72.94 - 105.84)	24	93.80 (78.89 - 111.53)
Study GSP 301-102						
GSP 301-1 NS vs Mometasone furoate NS QD (mometasone furoate in GSP 301 NS vehicle)	28	113.83 (96.97 - 133.61)	22	118.36 (103.73 - 135.05)	17	118.50 (104.79 - 134.01)
GSP 301-1 NS vs NASONEX	29	141.84 (121.68 - 165.34)	26	109.92 (95.49 - 126.53)	19	115.14 (101.77 - 130.28)

AUC_∞=area under the plasma concentration versus time curve from time 0 to infinity; AUC_t=area under the plasma concentration versus time curve from time 0 to the last measurable concentration; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = Geometric mean ratio; N = number of subjects; NS = nasal spray
Source: Table 2 Table 3 Table 6 and Table 7.

Study GSP 301-301 was performed with the final commercial formulation and characterizes the systemic exposure with the intended dose. This was a double-blind, randomized, parallel-group, comparative study to evaluate the efficacy and safety of GSP 301 NS administered as two sprays/nostril BID compared with GSP 301 placebo NS and individual monotherapy formulations of Glenmark olopatadine HCl NS and Glenmark mometasone furoate NS at the same dose and in the same vehicle in in adults and adolescents ≥12 years old with SAR. Rich-PK sampling was conducted in a subgroup of subjects, and sparse sampling was performed in all randomized subjects.

After repeated intranasal administration of 2 sprays per nostril BID (2660 µg of olopatadine HCl and 100 µg of mometasone furoate) of GSP 301 NS in subjects with SAR, the mean (± SD) C_{max} was 9.92 ± 3.74 pg/mL for mometasone furoate, and the mean AUC_{tau} was 58.40 ± 27.00 pg·h/mL. For olopatadine, C_{max} was 19.80 ± 7.01 ng/mL, and the mean AUC_{tau} was 88.77 ± 23.87 ng·h/mL. Median t_{max} was 1 hour for both substances.

No comparison to the commercial monocomponents was included in this study, but there was a comparison to the nasal spray with the same composition as the fixed-dose combination but with only one active substance included. For olopatadine, similar exposure compared to the monocomponent was obtained, as in study GSP 301-101. For mometasone furoate, the exposure with the FDC was higher compared to the exposure with the monocomponent, while study GSP-301-102 demonstrated comparable exposure for FDC (previous formulation) and monocomponent. The applicant claims that this may be due to higher inter-subject variability seen with mometasone monotherapy in study GSP 301-301, which may be the case. Anyhow, based on study GSP-301-102 (single dose study in healthy volunteers) there is no indication on a significant effect of olopatadine on mometasone furoate pharmacokinetics, and this result is considered relevant also for the commercial formulation.

The applicant has also compared the results from this study to the PK data available in the SmPC for Patanase, and it is agreed that the results are comparable. Since no exposure data was available for Nasonex, the applicant compared the results from this study to the results for Nasonex in the phase 1 study GSP 301-102 (extrapolated to steady state and with comparison of AUC_{0-24} considering BID dosing in the phase 3 study). It is agreed that AUC_{0-24} is comparable, while C_{max} is lower with the FDC, which is not unexpected considering that a lower dose of mometasone furoate per occasion is

given with the FDC compared to Nasonex (100 microgram BID instead of 200 microgram QD).

Bioequivalence and influence of food
Since the pivotal phase 3 studies were performed with the final fixed dose combination formulation, there is no need for a pivotal bioequivalence study. The relative bioavailability studies (performed with a previous formulation which is the same as the final formulation except for the mometasone dose) is considered sufficient in order to bridge to pharmacokinetic data for the monocomponents. There is also PK data with the final formulation from the phase 3 study GSP 301-301 as discussed above. No influence of food is expected for this intranasal product with topical effect.

ADME, special populations and interactions
Acceptable references were provided for olopatadine and mometasone furoate data.

The apparent volumes of distribution of olopatadine and mometasone furoate were determined in the popPK analysis. V2/F and V3/F of olopatadine were 105 L and 325 L, respectively, whereas V2/F and V3/F of mometasone furoate were 3540 L and 47700 L, respectively.

Following single-dose intranasal administration of a combination of olopatadine and mometasone furoate, the mean elimination half-life for olopatadine was 8.63 (SD 5.88) hours (study GSP-301-101). CL/F was 28.1 L/h in the popPK analysis.
Following single dose intranasal administration of a combination of olopatadine and mometasone furoate, the elimination half-life of mometasone furoate was 18.11 hours (SD 5.84) (study GSP-301-102). CL/F was 1870 L/h in the popPK analysis.

Olopatadine is mainly eliminated through urinary excretion. Of the drug-related material recovered within the first 24 hours in the urine, 86% was unchanged olopatadine with the balance comprised of olopatadine N-oxide and N-desmethyl olopatadine. Olopatadine is not extensively metabolized, with at least 6 minor metabolites circulate in human plasma upon oral administration. The metabolites are formed by CYP3A4, FMO1 and FMO3.

Any portion of a mometasone furoate dose, which is absorbed, undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Metabolites are excreted mostly via the bile, and to a limited extent, into the urine.

Accumulation was negligible for olopatadine in the phase III study, and minimal accumulation was observed for mometasone furoate, in line with its half-life. For olopatadine and mometasone, the inter-individual variability in CL, Q, V_2 and V_3, ALAG1 and KA were moderate to high.

Pharmacokinetics of GSP 301 NS was not evaluated in patients with hepatic or renal impairment. It is expected to be consistent with the PK profiles of individual monotherapy components.
No data is available regarding the effects of renal impairment on mometasone furoate pharmacokinetics. Given the very low bioavailability of mometasone furoate and its limited excretion in urine, the lack of renal impairment study is acceptable.

After oral administration of olopatadine to the patients with renal impairment, before haemodialysis, at a single dose of 10mg, the pharmacokinetics of the unchanged drug were compared with that after administration to healthy male volunteers at a dose of 10mg. The Cmax value in patients before haemodialysis was 2.3-fold higher than that in healthy male volunteers. The AUC0-∞ and t1/2 values in patients with renal impairment were 8-fold higher and 1.3-fold longer, respectively, than those values in healthy male volunteers.
Considering that systemic exposure is expected to be considerably lower than after 20 mg oral doses, twice daily, which were safe and well-tolerated, the lack of dose adjustment in patients with renal impairment is acceptable.

According to the Nasonex USPI, administration of a single inhaled dose of 400 µg mometasone

furoate to subjects with mild, moderate, and severe hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50 to 105 pg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment. No literature was available in the public domain to support this claim, this is however consistent with numerous mometasone containing products. The SmPC text and the lack of dose adjustment in patients with hepatic impairment is therefore accepted, also considering the generally low systemic concentrations of mometasone furoate upon nasal inhalation.

No specific pharmacokinetic study examining the effect of hepatic impairment on olopatadine PK was conducted. As olopatadine is mainly excreted unchanged in urine, it is agreed that no dose adjustment is expected, and the lack of hepatic impairment study is acceptable.

Based on the popPK analysis, no significant effect of gender, race, weight or age on CL was observed. There were issues identified with the popPK models and therefore the results of the covariate analysis should be interpreted with caution. No dose adjustment is required. No dose adjustment is required in adolescents in the ages 12-17 years. Efficacy and safety in adolescents (> 12 years) were established in the Phase III studies. There is also one clinical study performed in children 6 to 11 years of age, given half of the dose recommended in adults and adolescents, but no indication is sought for this population.

The absence of interaction between olopatadine and mometasone furoate was demonstrated in the relative bioavailability studies. The remaining claims rely on the literature for the respective monocomponents.

The interaction potential of olopatadine, both regarding its effect on other medicinal products or their effect on olopatadine is considered low. Furthermore, potential effects of other medicinal products on GSP 301 NS are expected to be of low clinical relevance considering the local effect.
No information on the effect of mometasone furoate on other medicinal products was presented. This is acceptable, given the very low systemic bioavailability of mometasone furoate. The claim regarding the co-administration with CYP3A inhibitors arises from PRAC recommendations and does not require further literature. The applicant based a claim on the lack of interaction between mometasone and loratadine on an efficacy study with no PK data. As Ryaltris already contains an anti-histaminic component, this study is not sufficient to support this SmPC claim, thus the claim was removed.

In study GSP 301-301 steady systemic exposures of mometasone furoate and olopatadine attained with the final formulation of GSP 301 NS and the suggested clinical dose were as follows:
For mometasone furoate, C_{max} was 9.92 pg/mL and AUC_{tau} was 58.40 ng*h/ml, corresponding to a AUC_{0-24} of 116.8 pg*hr/mL.
For olopatadine, C_{max} was 19.8 ng/ml and AUCtau 88.77 ng*h/ml, corresponding to a AUC_{0-24} of 177.54 ng*h/ml.

IV.3 Pharmacodynamics

Olopatadine is a histamine H1-receptor antagonist. Mometasone furoate is an synthetic corticosteroid. The applicant makes reference to approved medicinal products for pharmacodynamic data. It can be concluded that no pharmacodynamic studies have been performed specifically with the FDC and no relevant data has been retrieved from literature. The pharmacodynamic effects of olapatadine HCl and mometasone furoate individually is considered well established (and widely available in SmPCs from products with the same API). Based on presented non-clinical and clinical data no specific concern related to a pharmacodynamic interaction is raised.

IV.4 Clinical efficacy

In allergic rhino-conjunctivitis trials primary measures of efficacy are patient self-rated symptom scores. Symptom scores should be collected at baseline and daily over the course of the trial. In the included studies symptoms were scored on a 12-hour basis, in the morning (AM) and evening (PM).

The EMA guideline states that there are no standardised and generally accepted scales for scoring nasal and eye symptoms/signs in SAR/PAR studies. However, reflective total nasal symptom score (rTNSS) has been widely used and is considered an adequate scoring scale for the primary endpoint.
For a FDC, confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the FDC is compared to its individual substances. Inclusion of a placebo group is recommended in guidelines and has been included in the pivotal studies.

Three main clinical studies are included in order to support the efficacy of Ryaltris in seasonal allergic rhinitis (SAR). Pooled data from these studies provides efficacy data for a total of 2971 patients with SAR.

The two confirmatory phase III studies demonstrated a statistically significant and clinically relevant treatment effects of the combination product Ryaltris on the primary endpoint, ie "change from baseline in average AM and PM subject-reported 12-hour rTNSS over the 14-day treatment period", in comparison to placebo. In addition, these pivotal studies provided sufficient total evidence of statistically significant and clinically relevant treatment effects of the combination product on the primary endpoint in comparison to the mono-components.

The applicant also included the secondary endpoint "Average AM and PM Subject-Reported Instantaneous Total Nasal Symptom Score (iTNSS)". This endpoint relates to the presence/severity of symptoms at the moment in the morning just prior to dosing (instantaneous rating, [i]) which is in contrast to the primary endpoint, reflective rating, [r] that is based on the previous 12 hours). Confirmatory phase III study GSP 301-304 showed statistically significant and clinically relevant treatment effects of the combination product Ryaltris on this secondary endpoint in comparison to placebo and mono-components.

SAR and PAR are alike in terms of disease mediators and manifestations, with differences between the two entities primarily based on the duration of the disease. 52-week data in PAR for AM rTNSS supports the efficacy findings in SAR and is overall in line with the other studied endpoints.
The applicant has also presented quality of life data which are in line with findings for the other endpoints and is thus considered supportive of the claimed efficacy.

Overall, the totality of the efficacy evidence is sufficient to support the approval of Ryaltris for the treatment of nasal symptoms associated with SAR and PAR in patients 12 years of age and older. However, the data for reflective ocular symptom score (rTOSS) does not demonstrate that Ryaltris is statistically better than the mono-component olopatadine. This negative finding is consistent across all three trials. For a FDC, superiority should be demonstrated over the mono-components in the claimed indication, i.e. treatment of nasal and ocular symptoms associated with allergic rhinitis and rhino-conjunctivitis.

IV.5 Clinical safety

Safety data from RCTs is available for 3062 subjects exposed to the proposed posology and the PAR-study provide valuable long-term 52-weeks safety data for 593 subjects. In total, the safety data base includes 4672 subjects. In the included studies, dysgeusia, epistaxis and nasal discomfort have been identified as common adverse events. Findings are consistent across studies. No clinically important findings have been reported for the investigated subgroups.
In the 52-week PAR study additional adverse events of upper respiratory tract infection, headache, viral upper respiratory tract infection, urinary tract infection and cough have been identified. It is noted that the difference between Ryaltris and placebo in the PAR study is small for respiratory tract infections (6.4% vs 6.1%), viral upper respiratory tract infections (2.3% vs 2.0%) and urinary tract infections (2.3% vs 2.0%). In this study, the observed risk for infections is thus modest, although an increased risk of respiratory infections could speculatively, based on the mode of action, be related to the corticosteroid mometasone. Overall, the reported common ADR are mainly local nasal reactions which could be expected to occur following the administration of a nasal spray. No clinically relevant changes in laboratory values have been detected in the clinical program.

Serious adverse events are rare in the study population with no alarming difference between groups. No deaths have been reported in the studies. Overall, this is considered reassuring for a nasal spray for SAR/PAR, which are relatively benign conditions.

IV.6 Risk Management Plans

Risk Management Plan
The MAH has submitted an updated risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ryaltris. The update is aligned with the request from the RMS in the D 70 preliminary assessment report and is considered acceptable.

Safety specification

Important identified risk(s)	• None
Important potential risk(s)	• None
Missing information	• Use in pregnancy and lactation

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 4 November 2020 is considered acceptable.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

For an FDC, such as Ryaltris (GSP 301), confirmatory clinical trials are necessary to prove efficacy, preferably by parallel group comparisons in which the FDC is compared to its individual substances. Inclusion of a placebo group is recommended in guidelines and has been included in the pivotal studies. Two main clinical studies are included in order to support the efficacy of GSP 301 NS in SAR, GSP 301-301 and GSP 301-304. Pooled data from these studies together with the dose finding phase 2 study GSP 301-201 provides efficacy data for a total of 2971 patients with SAR.

Overall, the totality of the efficacy evidence is sufficient to support the approval of Ryaltris for the treatment of nasal symptoms associated with SAR and PAR in patients 12 years of age and older.

However, the data for reflective ocular symptom score (rTOSS) does not demonstrate that Ryaltris is statistically better than the mono-component olopatadine. This null finding is consistent across all three trials. As previously stated, for an FDC, superiority should be demonstrated over the mono-components in the claimed indication, i.e. treatment of nasal and ocular symptoms associated with allergic rhinitis and rhino-conjunctivitis. The indication for ocular symptoms is therefore not approvable and has been deleted from the SmPC.

Safety data from RCTs is available for 3062 subjects exposed to the proposed posology and the PAR-study provide valuable long-term 52-weeks safety data for 593 subjects. In total, the safety data base includes 4672 subjects. Overall, the reported common ADR are mainly local nasal reactions which could be expected to occur following the administration of a nasal spray. Findings are consistent across studies. No clinically important findings have been reported for the investigated subgroups and no clinically relevant changes in laboratory values have been detected in the clinical program. Serious adverse events are rare in the study population with no alarming difference between groups. No deaths have been reported in the studies. Overall, this is considered reassuring for a nasal spray for SAR/PAR, which are relatively benign conditions.

The benefit-risk balance is deemed positive and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Description	Due date
The applicant has committed to submitting an updated ERA with three additional ERA studies (OECD TG106, OECD TG308 and OECD TG218) plus a Letter of Access for OECD TG234.	Q4 2023

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Ryaltris, 600 mg/25 mcg/actuation, nasal spray, suspension was positively finalised on 2021-04-13.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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