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SCHEDULING STATUS

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1. NAME OF THE MEDICINE

RYALTRIS (nasal spray)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RYALTRIS (nasal spray):

Each spray delivers:

600 µg olopatadine (as olopatadine hydrochloride) and 25 µg mometasone furoate (as mometasone furoate monohydrate).

Contains preservative: Benzalkonium chloride 0,02 % w/w.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

RYALTRIS is a nasal spray containing an isotonic aqueous white homogenous suspension in a metered dose manual spray unit free of lumps. It has a pH of approximately 3.7.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RYALTRIS is indicated for the treatment of symptoms associated with allergic rhinitis and rhinoconjunctivitis in patients 12 years of age and older.

4.2 Posology and method of administration

Posology:

The recommended dosage of **RYALTRIS** is 2 sprays in each nostril twice daily.

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Method of administration:

Administer **RYALTRIS** by the intranasal route only.

Shake the bottle well before each use.

Priming:

Prime **RYALTRIS** before initial use by releasing 6 sprays.

When **RYALTRIS** has not been used for 14 days or more, re-prime by releasing 2 sprays or until a fine mist appears.

Avoid spraying **RYALTRIS** into the eyes or mouth.

Components of RYALTRIS nasal spray:



Instructions for use:

1. Shake the bottle before use and remove the purple plastic over cap from the spray pump tip of the bottle.

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2. To prime the **RYALTRIS** pump before first use hold the nasal spray bottle firmly and upright with your index and middle finger on either side of the applicator (on finger rests) while supporting the grooved base of the bottle with your thumb. Push down on the pump quickly and firmly 6 times, releasing the spray into the air, away from the eyes and face, until a fine mist appears. If **RYALTRIS** is not used for 14 days, the bottle will need to be shaken and the pump primed with 2 sprays or until a fine mist appears. **RYALTRIS** is now ready for use.



3. Gently blow the nose to clear the nostrils.

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4. Shake the bottle well before each use (morning and evening). Hold the bottle firmly with the index and middle finger on either side of the applicator (on finger rests) while supporting the grooved base of the bottle with the thumb.



5. Close 1 nostril with a finger, insert the end of the nasal tip into the other nostril, while pointing it slightly toward the outside of the nose, away from the nasal septum.



6. Tilt the head forward slightly. Keep the bottle upright and press down once quickly and firmly on the finger rests to activate the pump. Breathe in gently through the nose as you spray. Then breath out through your mouth. Try not to get any spray in the eyes or directly on your nasal septum.



7. Repeat the above steps 4-6 and deliver a second spray in the same nostril.

8. Repeat with 2 sprays in the other nostril.

Avoid blowing your nose for the next 15 minutes.

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Do not tip your head back right after using to prevent **RYALTRIS** from going into your throat. After use, wipe the tip with a clean dry tissue or cloth.



Push the purple over cap back on the spray tip of the bottle until a noticeable click sound is heard.



Each bottle of **RYALTRIS** contains enough medicine for 7 or 14 days of regular use depending on the pack size (56 or 120 sprays after priming).

Unblocking of the RYALTRIS spray pump unit if it becomes clogged:

- Do not use a pin or any other sharp object to try and unblock the spray pump as it will cause damage resulting in an incorrect dose of medicine being delivered.

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- Instead, remove the spray pump unit by gently pulling upward. Remove the dust cap and place on the spray pump in warm water to soak.





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- After soaking for approximately 15 minutes, rinse both ends with warm tap water for 1- 2 minutes, and allow them to dry completely.



- When dry, place the dust cap on the spray pump tip and put the spray pump unit back on the bottle.



- Following the unblocking procedure, review the priming of the **RYALTRIS** pump before first use (Step 2) and re-prime using 2 sprays.
- Replace the over cap.
- Repeat the unblocking steps if needed.

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4.3 Contraindications

Hypersensitivity to olopatadine hydrochloride, mometasone furoate, or to any of the inactive ingredients of **RYALTRIS** (see *Section 6.1*).

Pregnancy and lactation.

Immunisation with live viral/bacterial vaccines.

Patients with active or quiescent Mycobacterium tuberculosis infections.

Patients with untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections irrespective of anatomical site (see *Section 4.4*).

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

Hypersensitivity reactions, including instances of wheezing, may occur after the intranasal administration of mometasone furoate monohydrate. Discontinue **RYALTRIS** if such reactions occur (see *Section 4.3*).

Immunosuppression:

RYALTRIS may suppress the immune system making the patient more susceptible to infections than healthy individuals. If exposed to chickenpox, prophylaxis with Varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective professional information for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral medicines may be considered.

RYALTRIS should not be used in patients with active or quiescent tuberculous infections of the respiratory tract, untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections, or ocular herpes simplex because of the potential for worsening of these infections (see *Section 4.3*).

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Caution is advised in treatment of patients with HIV infection.

Hypothalamic-pituitary-adrenal (HPA) axis effects:

Intranasal steroid products are designed to deliver drug directly to the nasal mucosa in order to minimise overall systemic glucocorticoid exposure and side effects. When intranasal corticosteroids are used at higher-than-recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. Medical practitioners should be alert for evidence of systemic effects, especially in chronically treated patients.

However, there is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with mometasone furoate nasal spray. Care must be taken while transferring patients from systemic steroid treatment to **RYALTRIS** if there is any reason to suppose that their adrenal function is impaired.

During transfer from systemic corticosteroids to intranasal corticosteroids some patients may experience symptoms of withdrawal from systemically active corticosteroids (e.g. joint and/or muscular pain, lassitude, and depression initially) despite relief from nasal symptoms. Such transfer may also unmask pre-existing allergic conditions such as allergic conjunctivitis and eczema, previously suppressed by systemic corticosteroid therapy.

Local nasal effects:

Instances of nasal ulceration and nasal septal perforation have been reported (see *Section 4.8*).

Instances of epistaxis have been reported (see *Section 4.8*).

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Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should avoid the use of **RYALTRIS** until healing has occurred.

In clinical studies with mometasone furoate administered intranasally, localised infections of the nose and pharynx with *Candida albicans* have occurred. When such an infection develops, it may require treatment with appropriate local therapy and discontinuation of treatment with **RYALTRIS**.

Glaucoma and cataracts:

The use of nasal corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Effect on growth:

Intranasal corticosteroids as in **RYALTRIS** may cause a reduction in growth velocity when administered to patients less than 18 years of age and the growth of patients less than 18 years of age receiving **RYALTRIS** should be monitored (see Pharmacokinetic properties, Special populations, Paediatric use).

Somnolence:

Somnolence has been reported following administration of **RYALTRIS** in clinical studies (see *Section 4.8*).

Concurrent use of **RYALTRIS** with alcohol or other central nervous system (CNS) depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

4.5 Interaction with other medicines and other forms of interaction

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No formal pharmacokinetic medicine interaction studies have been performed with **RYALTRIS**. Any medicine interactions from the combination of olopatadine and mometasone furoate are expected to reflect those of the components taken individually, as no pharmacokinetic interaction between olopatadine and mometasone furoate was observed when administered in combination.

*Olopatadine as contained in **RYALTRIS**:*

Medicine interactions with inhibitors of liver enzymes are not anticipated because olopatadine is eliminated predominantly by renal excretion. Olopatadine did not inhibit the *in vitro* metabolism of specific substrates for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Based on these data, medicine interactions involving P450 inhibition are not expected. Due to the modest protein binding of olopatadine (55 %), medicine interactions through displacement from plasma proteins are also not expected.

*Mometasone furoate as contained in **RYALTRIS**:*

Studies have shown that mometasone furoate, a component of **RYALTRIS**, is primarily and extensively metabolised to multiple metabolites in the liver. *In vitro* studies have confirmed the primary role of cytochrome P450 (CYP) 3A4 in the metabolism of mometasone furoate. Coadministration with ketoconazole, a potent CYP3A4 inhibitor, may increase the plasma concentrations of mometasone furoate.

4.6 Fertility, pregnancy and lactation

Pregnancy

RYALTRIS is contraindicated during pregnancy (see *Section 4.3*). Animal studies revealed evidence of embro-foetal toxicity and malformations.

Breastfeeding:

RYALTRIS is contraindicated in lactation.

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RYALTRIS is not for use by mothers who are breastfeeding their infants (see *Section 4.3*). Corticosteroids such as mometasone furoate are excreted in breast milk.

4.7 Effects on ability to drive and use machines

RYALTRIS may cause side effects such as somnolence and dizziness (see *Section 4.8*). Patients should be cautioned against engaging in hazardous activities requiring complete mental alertness and motor coordination, such as operating machinery or driving a motor vehicle, after administration of **RYALTRIS**.

4.8 Undesirable effects

The safety data described below reflects exposure to **RYALTRIS** in 3 062 patients with seasonal allergic rhinitis in 4 placebo- and active-controlled clinical studies of 2-week duration.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

System Organ Class	Frequency	Undesirable effect
Infections and infestations	*Uncommon*	Pharyngitis, respiratory tract infection
Nervous system disorders	*Common*	Dysgeusia (unpleasant taste)
	Uncommon	Dizziness, lethargy, somnolence, anxiety, insomnia
Respiratory, thoracic and mediastinal disorders	*Uncommon*	Cough, nasal dryness, nasal discomfort, throat irritation, wheezing
Gastrointestinal disorders	*Uncommon*	Dry mouth, abdominal discomfort, vomiting

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Skin and subcutaneous tissue disorders	*Uncommon*	Rash, pruritus, contact dermatitis

Description of selected adverse reactions

Local corticosteroid use as in **RYALTRIS** may result in the following:

- Nasal ulcerations, nasal septal perforations, epistaxis, impaired wound healing, and Candida albicans infection (see *Section 4.4*).
- Glaucoma and cataracts (see *Section 4.4*).
- Immunosuppression (see *Section 4.4*).
- HPA axis effects, including growth reduction (see *Section 4.4*).
- Somnolence (see *Section 4.4*).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/ risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online:

https://primaryreporting.who-umc.org/Reporting/Reporter

4.9 Overdose

The risks associated with overdosage for the individual components described below apply to **RYALTRIS**.

Olopatadine:

Symptoms of antihistamine overdose may include drowsiness in adults and, initially, agitation and restlessness, followed by drowsiness in children. There is no known specific antidote to olopatadine

hydrochloride. Should overdose occur, symptomatic or supportive treatment is recommended, taking into account any concomitantly ingested medications.

Mometasone furoate:

Chronic overdosage with **RYALTRIS** may result in signs or symptoms of hypercorticism (see *Section 4.4*).

5. PHARMACOLOGICAL PROPERTIES

5.2 Pharmacodynamic properties

A 21.5.1 Corticosteroids and analogues

The nasal spray formulation contains olopatadine hydrochloride and mometasone furoate.

Olopatadine is a histamine H1 receptor antagonist.

Mometasone furoate is a corticosteroid with anti-inflammatory properties. The precise mechanism of corticosteroid action on allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g. mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

5.3 Pharmacokinetic properties:

Absorption:

After repeated intranasal administration of 2 sprays per nostril of the nasal spray formulation (2 400 µg of olopatadine hydrochloride and 100 µg of mometasone furoate) twice daily in patients with seasonal allergic rhinitis, the mean (± standard deviation) peak plasma exposure (C_{max}) was 19,80 ± 7,01 ng/mL for olopatadine and 9,92 ± 3,74 pg/mL for mometasone furoate, and the mean exposure over the dosing regimen (AUC_{tau}) was 88,77 ± 23,87 ng/mL*h for olopatadine and 58,40 ± 27,00

pg/mL*h for mometasone furoate. The median time to peak exposure from a single dose was 1 hour for both olopatadine and mometasone furoate.

The systemic bioavailability of olopatadine and mometasone furoate from the nasal spray formulation following intranasal administration was estimated to be comparable with olopatadine hydrochloride and mometasone furoate nasal sprays administered as monotherapies.

Distribution:

The protein binding of olopatadine was reported as approximately 55 % in human serum and independent of drug concentration over the range of 0,1 to 1 000 ng/mL. Olopatadine binds predominately to human serum albumin.

The *in vitro* protein binding for mometasone furoate was reported to be 98 % to 99 % in concentration range of 5 to 500 ng/mL.

Metabolism:

Olopatadine is not extensively metabolised. Based on plasma metabolite profiles following oral administration of [14C]olopatadine, at least 6 minor metabolites circulate in human plasma. Olopatadine accounts for 77 % of peak plasma total radioactivity and all metabolites amounted to < 6 % combined.

Studies have shown that any portion of a mometasone furoate dose that is swallowed and absorbed undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Upon in vitro incubation, one of the minor metabolites formed is 6ß-hydroxy-mometasone furoate. In human liver microsomes, the formation of the metabolite is regulated by CYP3A4.

Elimination:

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Following single dose intranasal administration of a combination of olopatadine and mometasone furoate, the mean elimination half-lives of olopatadine and mometasone furoate were 8,63 and 18,11 hours, respectively.

Olopatadine is mainly eliminated through urinary excretion. Approximately 70 % of a [14C]olopatadine hydrochloride oral dose was recovered in urine with 17 % in the faeces. Of the medicine-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.

Following intravenous administration, the effective plasma elimination half-life of mometasone furoate was 5,8 hours. Any absorbed medicine is excreted as metabolites mostly via the bile, and to a limited extent, via the urine.

Special populations:

No pharmacokinetic studies were performed in special populations with the nasal spray formulation. The pharmacokinetics of the combination of olopatadine and mometasone furoate is expected to reflect that of the individual components, as the pharmacokinetics of the combination was found to be comparable to the individual components.

Hepatic impairment:

No specific pharmacokinetic study examining the effect of hepatic impairment was conducted. Metabolism of olopatadine via the liver is a minor route of elimination.

Administration of a single inhaled dose of 400 µg mometasone furoate to subjects with mild (n = 4), moderate (n = 4), and severe (n = 4) 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 appeared to increase with severity of hepatic impairment; however, few detectable levels were observed.

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Based on data from the individual components, no adjustment of the dosing regimen of the nasal spray formulation is warranted in patients with hepatic impairment.

Renal impairment:

The mean C_{max} values for olopatadine following single intranasal doses were not markedly different between healthy subjects (18,1 ng/mL) and patients with mild, moderate, and severe renal impairment (ranging from 15,5 to 21,6 ng/mL). Mean plasma AUC0-12 was 2-fold higher in patients with severe impairment (creatinine clearance < 30 mL/min/1,73 m^2). In these patients, peak steady-state plasma concentrations of olopatadine were approximately 10-fold lower than those observed after higher, 20 mg oral doses, twice daily, which were well tolerated.

The effects of renal impairment on mometasone furoate pharmacokinetics have not been adequately investigated.

Based on data from the individual components, no adjustment of the dosing regimen of the nasal spray formulation is warranted in patients with renal impairment.

Age:

The nasal spray formulation pharmacokinetics has not been investigated in patients under 12 years of age (see Paediatric use below). Based on population pharmacokinetic analysis among patients 12 years of age and older, the pharmacokinetics of olopatadine and mometasone furoate with the nasal spray formulation was not influenced by age.

Paediatric use:

Intranasal corticosteroids may cause a reduction in growth velocity in patients less than 18 years of age even in the absence of laboratory evidence of suppression of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the

impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied.

The growth of patients less than 18 years of age receiving intranasal corticosteroids including mometasone furoate should be monitored routinely (e.g. via stadiometry).

Use in elderly patients:

No overall differences in safety or efficacy were observed in data collected from 145 patients aged 65 years and older versus younger patients who were treated with the nasal spray formulation in placebo- and active-controlled studies.

Hepatic impairment:

No studies have been conducted with the nasal spray formulation in patients with hepatic impairment. However, there have been reports of concentrations of mometasone furoate appearing to increase with severity of hepatic impairment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carboxymethyl cellulose sodium, dibasic sodium phosphate heptahydrate, edetate disodium, microcrystalline cellulose, polysorbate 80, sodium chloride, water for injection.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

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Store at or below 25 °C.

Store upright with over cap. Do not freeze or refrigerate.

Do not use after the expiry date printed on the bottle.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

A white opaque HDPE round bottle, crimp neck with base cap, having curved ribs at the bottom, crimp-sealed with a nasal spray pump and fitted with a white actuator and purple over cap and packed in an outer carton.

Each bottle contains 56 or 120 metered sprays depending on the pack size.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Glenmark Pharmaceuticals South Africa (Pty) Ltd

34 Monte Carlo Crescent,

Block A, First floor,

Kyalami Park, Midrand,

1684

8. REGISTRATION NUMBER(S)

53/21.5.1/0457

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5 May 2020

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10. DATE OF REVISION OF TEXT

18 July 2022