SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

SEREHALE 50/100

SEREHALE 50/250

SEREHALE 50/500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

SEREHALE contains Fluticasone propionate and Salmeterol xinafoate as active ingredients.

SEREHALE 50/100: Fluticasone propionate/Salmeterol/ELPEN inhalation powder pre-dispensed (100+50) mcg/blister: 100 mcg Fluticasone propionate/blister & 50 mcg Salmeterol/blister.

SEREHALE 50/250: Fluticasone propionate/Salmeterol/ELPEN inhalation powder pre-dispensed (250+50) mcg/blister: 250 mcg Fluticasone propionate/blister & 50 mcg Salmeterol/blister.

SEREHALE 50/500: Fluticasone propionate/Salmeterol/ELPEN inhalation powder pre-dispensed (500+50) mcg/blister: 500 mcg Fluticasone propionate/blister & 50 mcg Salmeterol/blister.

Contains: Sugar (lactose monohydrate).

SEREHALE 50/100: Fluticasone Blister (1st Blister) contains 12,40 mg of Lactose monohydrate and Salmeterol blister (2nd Blister) contains 12,43 mg of Lactose monohydrate.

SEREHALE 50/250: Fluticasone Blister (1st Blister) contains 12,25 mg of Lactose monohydrate and Salmeterol blister (2nd Blister) contains 12,43 mg of Lactose monohydrate.

SEREHALE 50/500: Fluticasone Blister (1st Blister) contains 12,00 mg of Lactose monohydrate and Salmeterol blister (2nd Blister) contains 12,43 mg of Lactose monohydrate.

For full list of excipients, **see section 6.1.**

3. PHARMACEUTICAL FORM:

Inhalation powder

SEREHALE 50/100, 50/250, 50/500 A white plastic device, containing 60 alu-alu strips with two blisters each containing white powder. One blister contains Fluticasone propionate and lactose monohydrate and the second blister contains Salmeterol xinafoate and lactose monohydrate.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

SEREHALE Accuhaler is indicated in regular prophylactic treatment of atopic asthma in children and adults, who have been stabilized on identical dosages of the components of **SEREHALE** given concurrently.

Chronic Obstructive Pulmonary Disease (COPD):

SEREHALE Accuhaler is indicated for the regular treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.
SEREHALE is indicated for symptomatic treatment of patients with severe COPD (FEV1 <50 % predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy.

4.2 Posology and method of administration

Posology

Patients should be made aware that **SEREHALE** Accuhaler must be used regularly for optimum benefit even when asymptomatic.

Patients should be regularly reassessed by health care provider. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

SEREHALE Accuhaler is not for relief of acute symptoms for which a fast and short-acting bronchodilator is required. Patients should always be advised to have their relief medicine available at all times.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patients should be reviewed. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of **SEREHALE** Accuhaler has failed to give adequate control of reversible obstructive airways disease, the patient should be reviewed. Consideration should be given to additional corticosteroid therapies, and to including administration of antibiotics if an infection is present.

Recommended doses:

Adults and adolescents 12 years and older:

- One inhalation (**SEREHALE** 50/100 Accuhaler) twice daily, or
- One inhalation (**SEREHALE** 50/250 Accuhaler) twice daily, or
- One inhalation (**SEREHALE** 50/500 Accuhaler) twice daily.

COPD

Adults:

- One inhalation (**SEREHALE** 50/250 Accuhaler) or one inhalation (**SEREHALE** 50/500 Accuhaler) twice daily.

Special population

There is no need to adjust the dose in elderly patients or in those with renal or hepatic impairment.

Paediatric population

Children 4 years and older:

- One inhalation (**SEREHALE** 50/100 Accuhaler) twice daily.

There are no data available for the use of **SEREHALE** Accuhaler in children under 4 years.

Method of administration

SEREHALE Accuhaler is for oral inhalation use only.

4.3 Contraindications

SEREHALE Accuhaler is contraindicated in patients with history of hypersensitivity to fluticasone propionate & salmeterol xinafoate or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

SEREHALE Accuhaler is not for relief of acute symptoms for which a fast and short-acting bronchodilator is required. Patients should be advised to have their relief medicine available at all times.

Increasing use of short-acting inhaled beta$_2$-acting agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient should be reassessed.

Sudden and progressive deterioration in asthma control is potentially life-threating and may have several causes. Consideration should be given to increasing corticosteroid dosage if not caused by otherwise treatable causes of deterioration.

Treatment with **SEREHALE** Accuhaler should not be stopped abruptly as adrenal insufficiency may be precipitated in this way.

Systematic corticosteroid effects may occur in patients on fluticasone treatment. Patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled fluticasone propionate.

Patients with severe asthma may require high dose inhaled (see section 4.2) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Patients weaned off oral steroids whose adrenocortical function is still impaired should carry systematic steroid warning card indicating that they may need supplementary systematic steroid during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

In cases inhaled therapy may unmask underlying eosinophilic conditions (e.g. Churg-Strauss syndrome). These cases have usually been associated with reduction

or withdrawal of oral corticosteroid therapy. A direct causal relationship has not been established.

Systematic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored.

Patients in medical or surgical emergency, who require high doses of inhaled steroids and/or intermittent treatment with oral steroids are at risk of impaired adrenal reserve.

The extent of the adrenal impairment may require specialist advice before elective procedures. The possibility of residual impaired adrenal response should always be borne in mind in emergency and elective situations likely to produce stress and appropriate corticosteroid treatment must be considered.

In children taking recommended doses of inhaled fluticasone propionate, adrenal function and adrenal reserve usually remain within the normal range. However, the possible effects of previous of previous or intermittent treatment with oral steroids should be discounted.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of inhaled fluticasone propionate or by giving a systematic steroid and/or an antibiotic if there is an infection.

Special care is necessary in patients with active or quiescent pulmonary tuberculosis. **SEREHALE** should be administered with caution in patients with thyrotoxicosis. Patients on corticosteroid therapy may have adrenocortical suppression.

Cardiovascular effects

Seretide may cause cardiac dysrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. Seretide should be used with caution in patients with severe cardiovascular disorders or heart rhythm abnormalities and in patients with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

Hyperglycaemia

There have been reports of increases in blood glucose levels (see section 4.8) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes, which may include cataract, glaucoma or diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Excipients

SEREHALE contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

β adrenergic blockers may weaken or antagonise the effect of salmeterol. Both non-selective and selective β blockers should be avoided unless there are compelling reasons for their use. Potentially serious hypokalaemia may result from β2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

Concomitant use of other β adrenergic containing medicines can have a potentially additive effect.

Fluticasone Propriate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome CYP3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome CYP3A4 inhibitor) 100 mg twice a day increased the fluticasone propionate plasma concentrations several hundred-fold, resulting in markedly reduced serum cortisol concentrations. Information about this interaction is lacking for inhaled fluticasone propionate, but a marked increase in fluticasone propionate plasma levels is expected. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side effects.

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole and cobicistat-containing products, and moderate CYP3A inhibitors, such as erythromycin, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side effects. Combinations

should be avoided unless the benefit outweighs the potential increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Salmeterol

Potent CYP3A4 inhibitors

Co-administration of ketoconazole (400 mg orally once daily) and salmeterol (50 micrograms inhaled twice daily) resulted in a significant increase in plasma salmeterol exposure (1.4-fold Cmax and 15-fold AUC). This may lead to an increase in the incidence of other systemic effects of salmeterol treatment (e.g. prolongation of QTc interval and palpitations) compared with salmeterol or ketoconazole treatment alone (see section 4.4).

Clinically significant effects were not seen on blood pressure, heart rate, blood glucose and blood potassium levels. Co-administration with ketoconazole did not increase the elimination half-life of salmeterol or increase salmeterol accumulation with repeat dosing.

The concomitant administration of ketoconazole should be avoided unless the benefits outweigh the potentially increased risk of systemic side effects of salmeterol treatment. There is likely to be a similar risk of interaction with other potent CYP3A4 inhibitors (e.g. itraconazole, telithromycin, ritonavir).

Moderate CYP 3A4 inhibitors

Co-administration of erythromycin (500 mg orally three times a day) and salmeterol (50 micrograms inhaled twice daily) in 15 healthy subjects for 6 days resulted in a

small but non-statistically significant increase in salmeterol exposure (1.4-fold C_{max} and 1.2-fold AUC). Co-administration with erythromycin was not associated with any serious adverse effects.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Fluticasone propionate

Safety in pregnancy has not been established.

Corticosteroids have been shown to be teratogenic in animals. As these medicines are absorbed when inhaled, teratogenicity following inhalation cannot be excluded.

Salmeterol

Safety in pregnancy has not been established.

Breastfeeding

Fluticasone propionate

Safety in lactation has not been established.

Salmeterol

Safety in lactation has not been established. There is no experience of the use of salmeterol in nursing mothers.

Fertility

There are no data available.

4.7 Effects on the ability to drive and use machines

SEREHALE is unlikely to produce an effect. **SEREHALE** causes visual disturbances.

4.8 Undesirable effects

As **SEREHALE** contains salmeterol and fluticasone propionate, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no incidence of additional adverse events following concurrent administration of the two compounds.

System Organ Class	**Frequency**	**Side effects**
Infections & Infestations	*Frequent*	Candidiasis of the mouth and throat, pneumonia (in COPD patients), bronchitis.
	Less frequent	Oesophageal candidiasis

Immune System Disorders	*Less frequent*	Hypersensitivity reactions with the following manifestations: Cutaneous hypersensitivity reactions, angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (Dyspnoea), respiratory symptoms (bronchospasm), anaphylactic reactions including anaphylactic shock.
Endocrine Disorders	*Less frequent*	Cushing's syndrome, cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density.
Metabolism & Nutrition Disorders	*Less frequent*	Hyperglycaemia
	Frequency unknown	Hypokalaemia

Psychiatric Disorders	*Less frequent*	Anxiety, sleep disorders, behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children)
	Frequency unknown	Depression, aggression (predominantly in children)
Nervous System Disorders	*Frequent*	Headache
	Less frequent	Tremor
Eye Disorders	*Less frequent*	Cataract, glaucoma
	Frequency unknown	Vision, blurred
Cardiac Disorders	*Less frequent*	Palpitations, tachycardia, cardiac arrhythmias (including supraventricular tachycardia and extrasystoles), atrial fibrillation, angina pectoris
Respiratory, Thoracic & Mediastinal Disorders	*Frequent*	Nasopharyngitis, throat irritation, hoarseness/dysphonia, sinusitis
	Less frequent	Paradoxical bronchospasm

Skin and subcutaneous tissue disorders	*Frequent*	Contusions
Musculoskeletal & Connective Tissue Disorders	*Frequent*	Muscle cramps, traumatic fractures, arthralgia, myalgia

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 under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The symptoms and signs of salmeterol overdose are tremor, headache and tachycardia. The preferred antidote for overdosage with salmeterol is a cardio-selective beta-blocking medicine. Both non-selective and selective beta-blockers should be avoided in patients with reversible obstructive airways disease unless there are compelling reasons for their use.

Acute: Inhalation of fluticasone propionate at dosages in excess of those recommended may lead to temporary suppression of adrenal function. This does

not necessitate emergency action being taken. In these patients treatment with fluticasone propionate by inhalation should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

Chronic: Use of inhaled fluticasone propionate at doses in excess of those recommended over prolonged periods may lead to some degree of adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment with inhaled fluticasone propionate should be continued at a dose sufficient to control asthma.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Category and class: A 21.5.1 Corticosteroids and analogues

Pharmacotherapeutic Group: Adrenergic in combination with corticosteroids or other drugs, excl. Anticholinergics, ATC Code: R03AK06.

Mechanism of action and pharmacodynamic effects:

SEREHALE contains salmeterol and fluticasone propionate which have differing modes of action.

Salmeterol:

Salmeterol is a selective long-acting (12 hour) β2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

Salmeterol produces a longer duration of bronchodilation, lasting for at least 12 hours, than recommended doses of conventional short-acting β2 agonists.

In man salmeterol inhibits the early and late phase response to inhaled allergen and after single dosing attenuates bronchial hyperresponsiveness.

Fluticasone propionate:

Fluticasone propionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, with less adverse effects than when corticosteroids are administered systemically.

5.2 Pharmacokinetic properties

For pharmacokinetic purposes, each component can be considered separately.

Salmeterol:

Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition, there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the medicine in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram /mL or less) achieved after inhaled dosing.

Fluticasone propionate:

The absolute bioavailability of a single dose of inhaled fluticasone propionate varies between approximately 5 to 11% of the nominal dose depending on the inhalation

device used. In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed.

Absorption

Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and presystemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

Distribution

The disposition of fluticasone propionate is characterised by high plasma clearance (1150 mL/min), a large volume of distribution at steady-state (approximately 300 L) and a terminal half-life of approximately 8 hours.

Plasma protein binding is 91%.

Metabolism/Elimination

Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also found in the faeces.

The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in faeces as metabolites and unchanged medicine.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 ˚C

Protect from moisture and sunlight.

6.5 Nature and contents of container

SEREHALE 50/100, 50/250, 50/500 Accuhaler Powder for Inhalation: A white plastic device, containing 60 alu-alu strips with two blisters each containing white powder, packed into a carton box together.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements

7. Holder of certificate of registration

Innovata Pharmaceuticals

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100 Northern Parkway

Ormonde

Johannesburg

2092

South Africa

8. Registration numbers

TBI

9. Date of first authorization/Renewal of the authorization

TBI

10. Date of revision of the text

TBI

REFERENCES:

1. Reference 1: Seretide® Accuhaler PI, GlaxoSmithKline South Africa (Pty) Ltd: 7 April 2006.
2. Reference 2: Seretide® 500 Accuhaler. SmPC

   Date of first authorisation/Date of renewal of authorisation: 1 February 1999/ 3 December 2008.

   Date of revision of the text: 18 November 2019.

   Name of registration holder; Glaxo Wellcome UK Ltd

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