Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SPIRODISC 50/100, powder for inhalation

SPIRODISC 50/250, powder for inhalation

SPIRODISC 50/500, powder for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SPIRODISC is supplied in a moulded plastic device containing a foil strip with 60 regularly spaced blisters. Each blister is a single inhalation which provides a dose of 50 micrograms of salmeterol (as salmeterol xinafoate) and 100, 250 or 500 micrograms of fluticasone propionate.

Excipients with known effect: Contains sugar (lactose monohydrate).
Each dose of SPIRODISC 50/100 contains 13,127 mg of lactose (as monohydrate).
Each dose of SPIRODISC 50/250 contains 12,877 mg of lactose (as monohydrate).
Each dose of SPIRODISC 50/500 contains 12,627 mg of lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for inhalation.

Plastic device containing an aluminium foil strip with 60 regularly placed blisters each containing a white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

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

Chronic Obstructive Pulmonary Disease

SPIRODISC is indicated for the regular treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.
SPIRODISC is indicated for the 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 SPIRODISC must be used daily for optimum benefit, even when asymptomatic.
Patients should be regularly reassessed by a doctor. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.
SPIRODISC 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 medication 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 patient should be reviewed. Consideration should be given to increasing corticosteroid therapy. Also, where the current dosage of SPIRODISC 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

Asthma

Adults and adolescents 12 years and older:

- One inhalation of SPIRODISC 50/100 twice daily, or
- One inhalation of SPIRODISC 50/250 twice daily, or
- One inhalation of SPIRODISC 50/500 twice daily.

Paediatric population

Children 4 years and older:

- One inhalation of SPIRODISC 50/100 twice daily.

There are no data available for use of SPIRODISC in children under 4 years.

Do not exceed the recommended dose.

Chronic Obstructive Pulmonary Disease (COPD)

For adult patients the recommended dose is one inhalation SPIRODISC 50/250 or one inhalation SPIRODISC 50/500 twice daily.

Do not exceed the recommended dose.

Special patient groups

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

Method of administration

SPIRODISC is for oral inhalation only.

4.3 Contraindications

- Hypersensitivity to salmeterol or fluticasone propionate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Deterioration of disease

SPIRODISC should not be used to treat acute asthma symptoms for which a fast- and short- acting bronchodilator is required. Patients should be advised to have their inhaler to be used for relief in an acute asthma attack available at all times.

Patients should not be initiated on SPIRODISC during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with SPIRODISC. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on SPIRODISC.

Increased requirements for use of reliever medication (short-acting bronchodilators), or decreased response to reliever medication indicate deterioration of control and patients should be reviewed by a doctor.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy if not caused by otherwise treatable causes of deterioration.

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of SPIRODISC. Regular review of patients as treatment is stepped down is important. The lowest effective dose of SPIRODISC should be used (see section 4.2).

For patients with COPD experiencing exacerbations, treatment with systemic corticosteroids is typically indicated, therefore patients should be instructed to seek medical attention if symptoms deteriorate with SPIRODISC.

Treatment with SPIRODISC should not be stopped abruptly in patients with asthma due to risk of exacerbation. Therapy should be down-titrated under supervision by a doctor. For patients with COPD cessation of therapy may also be associated with symptomatic decompensation and should be supervised by a doctor.

As with all inhaled medication containing corticosteroids, SPIRODISC should be administered with caution in patients with active or quiescent pulmonary

tuberculosis and fungal, viral or other infections of the airway. Appropriate treatment should be promptly instituted, if indicated.

Cardiovascular effects

SPIRODISC may cause cardiac dysrhythmias e.g. supraventricular tachycardia, extrasystoles and atrial fibrillation, and a mild transient reduction in serum potassium at high therapeutic doses. SPIRODISC 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 or in the presence of hypoxia and acidosis. SPIRODISC should also be used with caution if the medicine is administered concomitantly with other medicines that cause hypokalaemia and cardiac dysrhythmias.

Overdosage may cause cardiac effects. High doses may increase the risk of serious side effects, including cardiac dysrhythmias. The maximum dose should not be exceeded.

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.

Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated

straightaway. SPIRODISC should be discontinued immediately, the patient assessed, and alternative therapy instituted if necessary.

The pharmacological side effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

Excipients

SPIRODISC contains lactose monohydrate of up to 13,127 mg/dose. This amount does not normally cause problems in lactose intolerant people. The excipient lactose contains small amounts of milk proteins, which may cause allergic reactions.

Systemic corticosteroid effects

Systemic 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 Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract and glaucoma and less frequently, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see Paediatric population sub-heading below for information on the systemic effects of inhaled corticosteroids in children and adolescents). It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained.

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

Prolonged treatment of patients with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Cases of adrenal suppression and acute adrenal crisis have also been described with doses of fluticasone propionate between 500 and less than 1000 microgram. Situations, which could potentially trigger acute adrenal crisis include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, hypotension, decreased level of consciousness, hypoglycaemia, and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Therefore these patients should be treated with special care and adrenocortical function regularly monitored. Patients who have required high dose emergency corticosteroid therapy in the past may also be at risk. This possibility of residual impairment should always be borne in mind in emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment must be considered. The extent of the adrenal impairment may require specialist advice before elective procedures.

Ritonavir can greatly increase the concentration of fluticasone propionate in plasma. Therefore, concomitant use should be avoided. There is also an

increased risk of systemic side effects when combining fluticasone propionate with other potent CYP3A inhibitors (see section 4.5).

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Doctors should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Interactions with potent CYP3A4 inhibitors

Concomitant use of systemic ketoconazole significantly increases systemic exposure to salmeterol. This may lead to an increase in the incidence of systemic effects (e.g. prolongation in the QTc interval and palpitations). Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should therefore be avoided (see section 4.5).

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 rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Paediatric Population

Children and adolescents < 16 years taking high doses of fluticasone propionate (typically ≥ 1000 µg/day) may be at particular risk. Systemic effects may occur, particularly at high doses prescribed for long periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, acute adrenal crisis and growth retardation in children and adolescents and less frequently, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression. Consideration should be given to referring the child or adolescent to a paediatric respiratory specialist.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroid is regularly monitored. **The dose of inhaled corticosteroid should be reduced to the lowest dose at which effective control of asthma is maintained.**

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 β_2 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 Propionate

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 medicine interactions mediated by fluticasone propionate are unlikely.

CYP3A4 inhibitors

Ritonavir (a highly potent cytochrome CYP3A4 inhibitor) 100 mg b.i.d. administered with intranasal fluticasone 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.

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 CYP3A4 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. In case of a need for use, 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 microgram inhaled twice daily) resulted in a significant increase in plasma salmeterol exposure (1,4-fold C_{max} 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 microgram inhaled twice daily) 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 during 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 during lactation has not been established.

Salmeterol

There is no experience of the use of salmeterol in nursing mothers.

Fertility

There are no data in humans. However, animal studies showed no effects of salmeterol or fluticasone propionate on fertility.

4.7 Effects on ability to drive and use machines

SPIRODISC has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

As SPIRODISC 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**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations	Candidiasis of the mouth and throat, pneumonia (in COPD patients)[1,3], bronchitis[1]	Oesophageal candidiasis	
Immune system disorders		Hypersensitivity reactions with the following manifestations: Cutaneous hypersensitivity reactions,	

		respiratory symptoms (dyspnoea), angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (bronchospasm), anaphylactic reactions including anaphylactic shock	
Endocrine disorders		Cushing's syndrome, cushingoid features, adrenal suppression, growth retardation in children and adolescents, decreased bone mineral density[2]	
Metabolism and nutrition disorders	Hypokalaemia[1]	Hyperglycaemia[2]	

Psychiatric disorders		Anxiety, sleep disorders, behavioural changes, including psychomotor hyperactivity and irritability (predominantly in children)	Depression, aggression (predominantly in children)
Nervous system disorders	Headache	Tremor	
Eye disorders		Cataract, glaucoma[2]	Blurred vision[2]
Cardiac disorders		Palpitations, tachycardia, atrial fibrillation, angina pectoris, cardiac dysrrhythmias (including supraventricular tachycardia and extrasystoles).	
Respiratory, thoracic and mediastinal disorders	Nasopharyngitis[1], throat irritation, hoarseness/	Paradoxical bronchospasm	

	dysphonia, sinusitis[1]		
Skin and subcutaneous tissue disorders	Contusions[1]		
Musculoskeletal and connective tissue disorders	Muscle cramps, traumatic fractures[1], arthralgia, myalgia		

1. reported in patients with COPD

2. See section 4.4

3. See section 5.1.

Description of selected adverse reactions

The pharmacological side effects of β_2 agonist treatment, such as tremor, palpitations and headache, have been reported, but tend to be transient and reduce with regular therapy.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and should be treated straightaway. SPIRODISC should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Due to the fluticasone propionate component, hoarseness and candidiasis (thrush) of the mouth and throat and, less frequently, of the oesophagus can occur in some patients. Both hoarseness and incidence of mouth and throat candidiasis may be relieved by rinsing the mouth with water and/or brushing the teeth after using the product. Symptomatic mouth and throat candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the SPIRODISC.

Paediatric population

Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression and growth retardation in children and adolescents (see section 4.4). Children may also experience anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Salmeterol

The symptoms and signs of salmeterol overdosage 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.

Fluticasone propionate

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

Pharmacological Classification/ Category and Class: A 21.5.4 Corticosteroids – other combinations

Pharmacotherapeutic group: Adrenergics in combination with corticosteroids or other drugs, excl. Anticholinergics.

ATC Code: R03AK06

Mechanism of action and pharmacodynamic effects:

SPIRODISC contains salmeterol and fluticasone propionate which have differing modes of action. The respective mechanisms of action of both are discussed below.

Salmeterol

Salmeterol is a selective long-acting (12 hour) β_2 adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

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

Following oral administration 87-100 % of the dose is excreted in the faeces, up to 75 % as parent compound depending on the dose. There is a non-active major metabolite.

Following intravenous administration there is rapid plasma clearance suggestive of extensive hepatic extraction. The plasma elimination half-life is approximately 3 hours.

The volume of distribution is approximately 250 litres.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

The inhalation powder for 60 doses is contained in blisters held on a formed PVC coated base, with lidding foil. The strip is contained in a two-toned, circular plastic device.

The device is composed of a white body with a light blue (SPIRODISC 50/100), blue (SPIRODISC 50/250) or dark blue (SPIRODISC 50/500) coloured mouthpiece cap, and a red button. The device is further wrapped in a laminated foil pouch and packed into a cardboard box.

The device contains a dose counter which shows the number of doses remaining (60 to 1). To show when the last five doses have been reached, the number appears in red.

6.6 Special precautions for disposal and other handling

The inhaler releases a powder which is inhaled into the lungs. A dose indicator on the inhaler indicates the number of doses left. For detailed instructions for use of SPIRODISC, see the Patient Information Leaflet.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

SPIRODISC 50/100: 55/21.5.4/0278

SPIRODISC 50/250: 55/21.5.4/0279

SPIRODISC 50/500: 55/21.5.4/0280

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 February 2023

10. DATE OF REVISION OF THE TEXT

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