SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
COVOCORT, 10 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg hydrocortisone.

Contains sugar: lactose 148 mg per tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablets

White biconvex, scored tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Addison's disease or chronic adrenocortical insufficiency secondary to hypopituitarism.

4.2 Posology and method of administration
Posology
The normal dosage is 10 mg to 30 mg daily, in Addison's disease.

Method of administration
For oral administration.

4.3 Contraindications
- Hypersensitivity to hydrocortisone or to any of the excipients listed in section 6.1.
- Patients with peptic ulcer, osteoporosis, psychosis or severe psychoneuroses.
- Patients with systemic infections (unless specific anti-infective therapy is employed).
- In the presence of acute infections, including herpes zoster and herpes simplex ulceration of the eye.
- Patients with active or doubtfully quiescent tuberculosis.
- Concomitant vaccination with live vaccines.

4.4 Special warnings and precautions for use
Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of COVOCORT after prolonged therapy must therefore always be gradual, the rate depending upon the individual patient's response, the dose, and the duration of therapy.

During transient illnesses such as low grade infection, fever of any aetiology, stressful situations such as minor surgical procedures, the daily replacement dose must be increased temporarily. The patient must be carefully informed how to act in these situations and also advised to immediately seek medical attention should an acute deterioration occur; especially in the cases of gastroenteritis, vomiting and/or diarrhoea leading to fluid and salt loss, as well as inadequate absorption of COVOCORT. If COVOCORT has been stopped following prolonged therapy, it may need to be temporarily re-introduced.

Sudden withdrawal or reduction in dosage may precipitate acute adrenal insufficiency with symptoms such as malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 40 mg cortisone or equivalent) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about HPA-axis suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose equivalent to 40 mg cortisone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks, is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 200 mg daily of cortisone, or equivalent for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be considered even after courses lasting 3 weeks or less:

- patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks;
- when a short course has been prescribed within one year of cessation of long term therapy (months or years);
- patients receiving doses of systemic corticosteroid greater than 200 mg daily of cortisone (or equivalent);
- patients repeatedly taking doses in the evening.

Patients/and or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks maybe higher with high doses/systemic exposure (see section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most adverse reactions resolve after either dose reduction or withdrawal of the medicine, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.

Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Suppression of inflammatory response and immune function increases the susceptibility to infections and their severity. Infections may be masked and a feeling of well-being may be produced.

The clinical presentation can often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised. New infections may appear during their use. Scientific reports do not support immunosuppressive effects of hydrocortisone in doses that have been used for replacement therapy in patients with adrenal insufficiency. Therefore, there is no reason to believe that replacement doses of COVOCORT will exacerbate any systemic infection or worsen the outcome of such an infection.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunisation with varicella/zoster immunoglobulin (VZIG) is needed by exposed, non-immune patients who are receiving COVOCORT or who have used COVOCORT in the previous 3 months; should this be confirmed, the illness warrants specialist care and urgent treatment. COVOCORT should not be stopped and the dose may need to be increased.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Patients with concomitant adrenal insufficiency and retroviral infection, such as HIV, need careful dose adjustment due to potential interaction with antiretroviral medicines and increased COVOCORT dose due to the infection.

Live vaccines should not be given to individuals with impaired immune responsiveness caused by high doses of corticosteroids. Killed vaccines or toxoids may be given though their effects may be attenuated.

During acute adrenal insufficiency parenteral administration of hydrocortisone in high doses, together with sodium chloride 9 mg/ml (0,9 %) solution for injection, must be given.

Using higher than normal doses of COVOCORT, high (supra-physiological) dosages of hydrocortisone, can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Long-term treatment with higher than physiological hydrocortisone doses can lead to clinical features resembling Cushing´s syndrome with increased adiposity, abdominal obesity, hypertension and diabetes and thus result in an increased risk of cardiovascular morbidity and mortality.

Side effects result from excessive action on electrolyte balance, excessive action on other aspects of metabolism including gluconeogenesis, the action on tissue repair and healing and an inhibitory effect on the secretion of corticotrophin by the anterior lobe of the pituitary gland.

Particular care is required when prescribing COVOCORT in patients with the following conditions and frequent patient monitoring is necessary:

- hypertension or congestive heart failure;
- existing or previous history of severe affective disorders (especially previous history of steroid psychosis);
- diabetes mellitus (or a family history of diabetes);
- glaucoma (or family history or glaucoma). Prolonged use of high doses of glucocorticoids may produce posterior subcapsular cataracts, and glaucoma with possible damage to the optic nerves. Such effects have not been reported in patients receiving replacement therapy with glucocorticoids in doses used in adrenal insufficiency;
- previous corticosteroid-induced myopathy;
- liver failure;
- renal insufficiency, chronic renal failure and uraemia;
- epilepsy;
- recent myocardial infarction;
- infectious diseases;
- elderly patients.

During treatment, the patient should be observed for psychotic reactions, muscular weakness, electrocardiographic changes, hypertension and untoward hormonal effects.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or a previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

The insulin requirements of diabetic patients may be increased.

Patients with adrenal insufficiency should be monitored for thyroid dysfunction as both hypothyroidism and hyperthyroidism may markedly influence the exposure of administered COVOCORT.

Treatment of primary adrenal insufficiency often warrants addition of a mineralocorticoid.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. COVOCORT should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

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.

The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life threatening reactions.

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with malignancies, including haematological malignancies and solid tumours, following the use of systemic corticosteroids alone, including COVOCORT, or in combination with other chemotherapeutic medicines. Patients at high risk of TLS, such as patients with tumours that have a high proliferative rate, high tumour burden and high sensitivity to cytotoxic medicines, should be monitored closely and appropriate precautions should be taken.

Paediatric population
Corticosteroids cause growth retardation in infancy, childhood and adolescence; this may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time.

Excipients with known effect
COVOCORT contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take COVOCORT.

4.5 Interaction with other medicines and other forms of interaction
Potent CYP 3A4 inducers such as phenytoin, rifabutin, primidone, carbamazepine, aminoglutethimide, barbiturates (e.g. phenobarbital), rifampicin, St John's Wort and less potent inducers such as the antiretroviral medicines, efavirenz and nevirapine, can enhance the metabolic clearance of cortisol, decrease terminal half-life and thus reduce circulating

levels and increase fluctuations of cortisol (due to shorter terminal half-life). This may require dose adjustment of COVOCORT.

Mifepristone may reduce the effect of corticosteroids for 3-4 days.

Potent CYP 3A4 inhibitors such as ketoconazole, itraconazole, posaconazole, voriconazole, erythromycin, telithromycin, clarithromycin, ritonavir and grapefruit juice can inhibit the metabolism of COVOCORT and thus increase blood levels. During long-term prophylactic treatment with any of the antibiotics, adjustment of the dosage of COVOCORT should be considered.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side effects.

Oestrogens and other oral contraceptives increase the plasma concentration of corticosteroids and dosage adjustments may be required if oral contraceptives are added to or withdrawn from a stable dosage regimen.

The growth promoting effect of somatropin may be inhibited by the concomitant use of corticosteroids.

The desired actions of hypoglycaemic drugs (including insulin), antihypertensives and diuretics are antagonised by corticosteroids.

The effectiveness of coumarin anticoagulants may be affected by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Serum levels of salicylates, such as aspirin and benorilate, may increase considerably if corticosteroid therapy is withdrawn, possibly causing intoxication. Concomitant use of salicylates or of non-steroidal anti-inflammatory drugs (NSAIDs) with corticosteroids increases the risk of gastrointestinal bleeding and ulceration.

The potassium-depleting effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced by corticosteroids and signs of hypokalaemia should be looked for during their concurrent use. The risk of hypokalaemia is increased with theophylline and amphotericin. Corticosteroids should not be given concomitantly with amphotericin, unless required to control reactions.

The risk of hypokalaemia also increases if high doses of corticosteroids are given with high doses of sympathomimetics e.g. bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline. The toxicity of cardiac glycosides e.g. digoxin, is increased if hypokalaemia occurs.

Concomitant use with methotrexate may increase the risk of haematological toxicity.

High doses of corticosteroids impair the immune response and so live vaccines should be avoided (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual medicines; however, COVOCORT readily crosses the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development.

There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but it is usually resolved spontaneously following birth and is rarely clinically important. When treatment with corticosteroids is essential, patients with normal pregnancies may be treated as though they were in the non-gravid states.

Breastfeeding
COVOCORT is excreted in breast milk. Doses of up to 200 mg daily of cortisone are unlikely to cause systemic effects in the infant.

Infants of mothers taking higher doses than this may have a degree of adrenal suppression and the mother should be counselled if breast feeding is suitable.

Fertility
Patients with adrenal insufficiency have been shown to have reduced parity, which is most likely due to the underlying disease, but there is no indication that COVOCORT in doses for replacement therapy will affect fertility.

4.7 Effects on ability to drive and use machines
COVOCORT may cause sedation, vertigo, changes in vision, fatigue or muscle weakness. If you have any of these symptoms you should not drive or operate machinery.

4.8 Undesirable effects
a. Summary of the safety profile
The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the medicine, dosage, timing of administration and the duration of treatment (see section 4.4).

b. Tabulated summary of adverse reactions

System organ class	Frequency	Undesirable effects
Infections and infestations	Not known	Gastroenteritis, upper respiratory tract infection, viral infection, increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis, activation of fungal and viral infections including herpes
Blood and lymphatic system disorders	Not known	Decreased circulating lymphocytes, leucocytosis
Immune system disorders	Not known	Hypersensitivity, anaphylaxis
Metabolism and nutrition disorders	Not known	Negative protein and calcium balance, sodium and fluid retention, oedema tendency, hypokalaemic alkalosis, hypokalaemia, increased appetite
Psychiatric disorders [(a)]	Common	A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile

		mood and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbance, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia have been reported
Nervous system disorders	Not known	Aggravation of epilepsy, sedation, increased intracranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal
Eye disorders	Not known	Increased intraocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, dry eye, exacerbation of ophthalmic viral or fungal diseases, blurred vision, (see also section 4.4)
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Myocardial rupture following recent myocardial infarction, hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders	Not known	Hypertension, thromboembolism
Gastrointestinal disorders	Not known	Dyspepsia, peptic ulceration with perforation and haemorrhage, deterioration of existing gastric ulcer, abdominal distension, oesophageal ulcer, oesophagitis, upper abdominal pain, tooth erosion, candidiasis, acute pancreatitis, nausea
Skin and subcutaneous tissue disorders	Not known	Impaired healing, skin atrophy, contusion, ecchymosis, skin striae, pruritic rash, Cushing-like symptoms, acne, flushing, hirsutism, telangiectasia
Musculoskeletal and connective tissue disorders	Not known	Muscular weakness, proximal myopathy, osteoporosis, spontaneous fractures, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, joint swelling
General disorders and administration site conditions	Not known	Malaise, fatigue
Endocrine disorders	Not known	Hyperhidrosis, suppression of the hypothalamo-pituitary-adrenal axis, growth retardation in infancy, childhood and adolescence, Cushingoid facies (moon face, buffalo hump), induction of glucose intolerance or diabetes mellitus
Reproductive system and breast disorders	Not known	Amenorrhoea, irregular menstruation
Investigations	Not known	Increased weight, decreased high density lipoprotein, decreased blood potassium

[(a)] Reactions are frequent and may occur in both adults and children. In adults, the frequency of severe reactions have been estimated to be 5 % to 6 %. Psychological effects have been reported on withdrawal of corticosteroids and psychological dependence has occurred; the frequency is not known.

Withdrawal symptoms
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4). A withdrawal syndrome may also occur including pyrexia, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin modules and weight loss.

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
See section 4.8 for symptoms.

The adverse effects of hydrocortisone are nearly always due to its use in excess of normal physiological requirements. They should be treated symptomatically, where possible the dosage should be reduced or the drug slowly withdrawn.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: A 21.5.1 Corticosteroids and analogues
ATC code: H02AB09 Glucocorticoids

Hydrocortisone is the main glucocorticoid secreted by the adrenal cortex.

Hydrocortisone is a glucocorticoid and the synthetic form of endogenously produced cortisol. Glucocorticoids are important steroids for intermediary metabolism, immune function, musculoskeletal and connective tissue, and the brain. Cortisol is the principal glucocorticoid secreted by the adrenal cortex.

Naturally-occurring glucocorticoids (hydrocortisone and cortisol), which also have salt-retaining properties, are used as replacement therapy in adrenal insufficiency. They are also used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition they modify the body's immune responses to diverse stimuli.

5.2 Pharmacokinetic properties
Absorption
Hydrocortisone given by mouth is readily absorbed from the gastrointestinal tract.

Distribution
Hydrocortisone is extensively bound to plasma proteins. In plasma, cortisol is bound to corticosteroid-binding globulin (CBG, also called transcortin) and albumin. The binding is about 90 %.

Biotransformation
Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms, such as tetrahydrocortisone and tetrahydrocortisol.

Elimination
Metabolites are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone. Hydrocortisone has a plasma half-life of about 100 minutes. Hydrocortisone (cortisol) is a lipophilic drug that is eliminated completely via metabolism with a low clearance and accordingly low intestinal and hepatic extraction ratios.

Hydrocortisone is eliminated completely by metabolism by 11ßHSD type 1 and type 2 enzymes and CYP 3A4 in the liver and in peripheral tissue. CYP 3A4 is involved in the clearance of cortisol by the formation of 6β-hydroxycortisol which is excreted in urine. The transport of cortisol across membranes is expected to be mediated mainly by passive diffusion and therefore renal and biliary clearances are negligible.

Special populations
Renal impairment
A small amount of cortisol is excreted in the urine unchanged (< 0,5 % of the daily production), meaning that cortisol is eliminated completely by metabolism. Since severe renal impairment may affect medicinal products completely eliminated via metabolism, dose adjustment may be needed.

Hepatic impairment
No study has been performed in patients with hepatic impairment, however data in the literature for hydrocortisone support that no dose adjustment is required in mild to moderate hepatic impairment. In case of severe hepatic impairment, the functional liver mass decreases and thus the metabolising capacity for hydrocortisone. This may require dose individualisation.

Paediatric population
No pharmacokinetic data are available in children or adolescents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose
Magnesium stearate
Starch

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 light and moisture.

6.5 Nature and contents of container
Containers with 100 tablets.

6.6 Special precautions for disposal and other handling
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)
U/21.5.1/211

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14 April 1988

10. DATE OF REVISION OF THE TEXT
20 December 2024

Botswana: S2 B9302950
Namibia: NS2 90/21.5.1/00112

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PI 31998 02/2025