SCHEDULING STATUS

S4

1. **NAME OF THE MEDICINE:**

   HYDROCORTISONE 10 INNOVATA

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

   HYDROCORTISONE 10 INNOVATA

   Each tablet contains 10 mg Hydrocortisone.

   Contains sugar: Lactose monohydrate 78,80 mg

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

3. **PHARMACEUTICAL FORM:**

   HYDROCORTISONE 10 INNOVATA Tablets:

   Oval flat beveled 8 x 5.25 mm, white, with imprinted “H” on one side and plain on other side.

4. **CLINICAL PARTICULARS:**

   4.1 Therapeutic Indications

   Addison's disease/chronic adrenocortical insufficiency secondary to hypopituitarism.

   4.2 Posology and method of administration

   Posology

   Adults

   The normal dosage is 10 to 30 mg daily, in Addison's disease.

   Method of administration

For oral administration.

4.3 Contraindications

HYDROCORTISONE 10 INNOVATA is contraindicated in:

- 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

Patients should carry 'steroid treatment' cards, which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, medicine, dosage, and the duration of treatment.

The lowest possible dosage of corticosteroids should be used and when reduction in dosage is possible, the reduction should be gradual.

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 may be higher with high doses/systemic exposure (see

also section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, 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.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or 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.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children receiving hydrocortisone tablets) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster. 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 systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of

chickenpox is confirmed, the illness warrants specialist care and urgent treatment.

Corticosteroids should not be stopped and the dose may need to be increased.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening medicine reactions due to amphotericin.

Moreover, there have been cases reported in which concomitant use of amphotericin and hydrocortisone was followed by cardiac enlargement and congestive failure.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Average and large dosages of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increase excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

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.

A report shows that the use of corticosteroids in cerebral malaria is associated with a prolonged coma and an increased incidence of pneumonia and gastro-intestinal bleeding.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation may occur. During prolonged corticosteroid therapy, these patients should receive prophylactic chemotherapy.

The use of hydrocortisone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis.

Corticosteroids should be used with caution in renal insufficiency, hypertension, diabetes or in those with a family history of diabetes, congestive heart failure, thrombophlebitis, exanthematous disease, chronic nephritis, acute glomerulonephritis, metastatic carcinoma, osteoporosis (postmenopausal patients are at special risk), severe affective disorders (particularly if there is a history of steroid-induced psychosis), epilepsy, previous steroid myopathy, glaucoma (or family history of glaucoma), myasthenia gravis, non-specific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer. Signs of peritoneal irritation following gastro-intestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent.

Fat embolism has been reported as a possible complication of hypercortisonism.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Prolonged courses of corticosteroids increase susceptibility to infections and their severity. The clinical presentation of infections may also be atypical. Corticosteroids may mask some signs of infection and some serious infection such as septicaemia and tuberculosis may reach an advanced stage before being recognised. There may be an inability to localise infection in patients on corticosteroids. Corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false negative results.

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

Corticosteroids may activate latent amoebiasis or strongyloidiasis or exacerbate active disease. Therefore, it is recommended that latent or active amoebiasis and strongyloidiasis be excluded before initiating corticosteroid therapy in any patient at risk of or with symptoms suggestive of either condition.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

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.

Corticosteroids may increase or decrease motility and number of spermatozoa.

Diabetes may be aggravated, necessitating a higher insulin dosage. Latent diabetes mellitus may be precipitated.

Menstrual irregularities may occur, and this possibility should be mentioned to female patients.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroids, especially when a patient has a history of medicine allergies.

Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinaemia.

Withdrawal:

Drug-induced secondary adrenocortical insufficiency may result from too rapid a withdrawal
of corticosteroids and may be minimised by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, corticosteroid therapy should be reinstated. If the patient is receiving steroids already, the dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently (see section 4.5).
Stopping corticosteroid after prolonged therapy may cause withdrawal symptoms, including fever, myalgia, arthralgia and malaise. In patients who have received more than physiological doses of systemic corticosteroids (approximately 30 mg hydrocortisone) for greater than three 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 hypothalamic-pituitary adrenal (HPA) suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 30 mg hydrocortisone 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 three weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 200 mg hydrocortisone for three 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 three weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than three weeks.
- when a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- patients receiving doses of systemic corticosteroid greater than 200 mg hydrocortisone.
- patients repeatedly taking doses in the evening.

Paediatric population

Corticosteroids cause growth retardation in infancy, childhood and adolescence. Treatment
should be limited to the minimum dosage in order to minimise suppression of the hypothalamo-pituitary-adrenal axis and growth retardation. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored.

HYDROCORTISONE 10 INNOVATA contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose -galactose malabsorption should not take HYDROCORTISONE 10 INNOVATA.

4.5 Interaction with other medicines and other forms of interaction

Drug interactions listed below have been reported in pharmacological doses of corticosteroids and may not occur at replacement therapy doses of corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia. There is an increased risk of gastro-intestinal bleeding and ulceration when corticosteroids are given with aspirin and NSAIDs, although topical NSAIDs do not generally interact with corticosteroids. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Corticosteroids reduce plasma concentrations of salicylate and such an interaction may occur with pharmacological doses of glucocorticoids.

Phenytoin, ephedrine, rifabutin, carbamazepine, barbiturates, rifampicin, primidone, sympathomimetics and aminoglutethimide may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels

and lessened physiological activity, thus requiring adjustment in corticosteroid dosage.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports of altered response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

Ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdraw (see section 4.4).

Corticosteroids antagonise the effects of diuretics. Glucocorticosteroids are necessary for free water clearance by the kidneys. When corticosteroids are administered concomitantly with potassium-depleting diuretics (e.g. acetazolamide, loop diuretics, thiazides), patients should be observed closely for development of hypokalaemia.

Moreover, corticosteroids may affect the nitroblue tetrazolium test for bacterial infection and produce false negative results.

Corticosteroids antagonise the hypotensive effects of beta-blockers, alpha-blockers, calcium channel blockers, clonidine, diazoxide, methyldopa, moxonidine, nitrates, nitroprusside, hydralazine, minoxidil, adrenergic neurone blockers, ACE inhibitors and angiotensin II receptor antagonists.

Corticosteroids increase risk of hypokalaemia when given with cardiac glycosides, e.g. digoxin, theophylline and high dose of beta[2]

sympathomimetics e.g. bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline.

There is an increased risk of hypokalaemia when corticosteroids are given with amphotericin. Concomitant use of amphotericin with corticosteroids should be avoided unless amphotericin is needed to control reactions.

The effect of corticosteroids may be reduced for 3-4 days after interaction with mifepristone.

The plasma concentration of corticosteroids is increased by oral contraceptives containing oestrogens. Interactions of combined oral contraceptives may also apply to combined contraceptive patches. In the case of hormone replacement therapy, low doses are unlikely to induce interactions.

Corticosteroids reduce absorption of calcium salts.

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

Corticosteroids antagonise hypoglycaemic effect of antidiabetics.

There is an increased risk of haematological toxicity when corticosteroids are given with methotrexate.

Corticosteroids may inhibit the growth promoting effect of somatropin.

High doses of corticosteroids impair immune response to vaccines, avoid concomitant use with live vaccines.

Corticosteroids possibly reduce the effects of sodium benzoate and sodium phenyl butyrate.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

4.6 Fertility, pregnancy, and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual medicines, however, hydrocortisone 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.

Pregnant patients should be monitored closely if they develop fluid retention or pre-eclampsia. Hypoadrenalism may, in theory, occur in the neonate

following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. When corticosteroids are

essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Breastfeeding

Hydrocortisone 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 Hydrocortisone in doses for replacement therapy will affect fertility.

4.7 Effects on the ability to drive and use machines

Hydrocortisone may cause vertigo, visual field loss and muscle wasting and weakness. If affected, patients should not drive or operate machinery (see section 4.8).

4.8 Undesirable effects

System organ class	Frequent	Less Frequent	Frequency Unknown
Infections and infestations			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			Decreased circulating lymphocytes, leucocytosis
Immune system disorders			Hypersensitivity, anaphylaxis
Metabolism and nutrition disorders			Negative protein and calcium balance, sodium and fluid retention, oedema tendency, hypokalemic alkalosis, hypokalaemia, increased appetite
Psychiatric disorders [(a)]	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			Aggravation of epilepsy, sedation, increased intracranial pressure with papilloedema in children (pseudotumour cerebri) usually after treatment withdrawal, malaise, vertigo, headache
Eye disorders			Increased intraocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, dry eye, exacerbation of ophthalmic viral or fungal diseases, vision, blurred, exophthalmos (see also section 4.4)
Ear and			Vertigo

labyrinth disorders			
Cardiac disorders			Myocardial rupture following recent myocardial infarction, hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders			Hypertension, thromboembolism
Respiratory, thoracic and mediastinal disorders			Hiccups
Gastrointestinal disorders			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			Impaired healing, skin atrophy, contusion, ecchymosis, skin striae, pruritic rash, petechiae, erythema, increased sweating, may suppress reactions to skin tests, other

			cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic oedema, Cushing-like symptoms, acne, flushing, hirsutism, telangiectasia, angioedema
Musculoskeletal and connective tissue disorders			Muscular weakness, proximal myopathy, osteoporosis, spontaneous fractures, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, joint swelling
General disorders and Administration site conditions			Malaise, fatigue
Endocrine disorders			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, decreased carbohydrate tolerance, increased or decreased motility and

			number of spermatozoa, development of Cushingoid state
Reproductive system and breast disorders			Amenorrhoea, irregular menstruation
Investigations			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 has 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 side effects

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Contact Innovata Pharmaceuticals: regulatory@innovata.co.za

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

PHARMACOGICAL CLASSIFICATION:

A 21.5.1 Corticosteroids and analogues

Pharmacotherapeutic group: Glucocorticoids ATC code: A10BA02

5.1 Pharmacodynamic properties

Hydrocortisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally-occurring and synthetic, which are readily absorbed from the gastro-intestinal tract.

Hydrocortisone is believed to be the principal corticosteroid secreted by the adrenal cortex. Naturally- occurring glucocorticosteroids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. 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 is readily absorbed from the gastro-intestinal tract and 90 % or more of the drug is reversibly bound to protein.

Distribution

The binding is accounted for by two protein fractions. One, corticosteroid-binding globulin is a glycoprotein; the other is albumin.

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.

6. Pharmaceutical particulars

6.1 List of excipients

Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose (PH-102), povidone (K-30).

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister inside the carton until required for use.

Store in original container to protect from light and moisture.

6.5 Nature and contents of container

30's: Packed in Alu-Opaque PVC blisters containing 10 tablets per blister. 3 blister strips packed in an outer carton with a package insert.

6.6 Special precautions for disposal and other handling

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

7. Holder of certificate of registration

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

A 59/21.5.1/0080

9. Date of first authorization/Renewal of the authorization

31/03/2026

10. Date of revision of the text

TBI