

New Zealand Data Sheet

1. PRODUCT NAME

Hydrocortisone 5 mg Tablets
Hydrocortisone 20 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hydrocortisone 5 mg Tablet contains 5 mg of hydrocortisone.
Each Hydrocortisone 20 mg Tablet contains 20 mg of hydrocortisone.

Excipient(s) with known effect

Hydrocortisone Tablets contain lactose monohydrate.
For the full list of excipients, *see Section 6.1.*

3. PHARMACEUTICAL FORM

Hydrocortisone 5 mg Tablet: white, round, biconvex tablet having a diameter of 6.5 mm.
Hydrocortisone 20 mg Tablet: white, round, biconvex tablet having a diameter of 7.94 mm, breakline on one face and dp logo on the other.

The score line on Hydrocortisone 20 mg Tablet is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Replacement therapy in Addison's disease or chronic adrenocortical insufficiency secondary to hypopituitarism.
- Inhibition of the secondary increase in ACTH secretion when aminoglutethimide is administered for breast or prostatic cancer.

4.2. Dose and method of administration

Dose

As replacement therapy

The normal requirement is 10-30 mg daily (usually 20 mg in the morning and 10 mg at night to mimic the circadian rhythm of the body).

As combination therapy with aminoglutethimide

A dosage of 40 mg daily, given as 10 mg with breakfast, 10 mg with dinner and 20 mg at bedtime is usually recommended.

Special populations

Elderly population

Steroids should be used cautiously in the elderly, since adverse effects are enhanced in old age, *see Section 4.4.*

When long term treatment is to be discontinued, the dose should be gradually reduced over a period of weeks or months, depending on dosage and duration of therapy, *see Section 4.4.*

Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose, or whenever possible, as a single morning dose on alternative days.

Frequent patient review is required to titrate the dose against disease activity.

Paediatric population

Treatment should be limited to the minimum dosage for the shortest possible time, *see Section 4.4.*

Method of Administration

For oral administration

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1
- Systemic infections unless specific anti-infective therapy is given
- Live virus immunisation.

4.4. Special warnings and precautions for use

Adrenal suppression

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. 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 cases of gastroenteritis, vomiting and/or diarrhoea leading to fluid and salt loss, as well as to inadequate absorption of oral hydrocortisone. If corticosteroids have been stopped following prolonged therapy, they may need to be temporarily re-introduced.

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

Anti-inflammatory / immunosuppressive effects and infection

Suppression of inflammatory response and immune function increases the susceptibility to infections and their severity. 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 hydrocortisone 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 systemic corticosteroids or who have used them the previous 3 months; should this be confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids 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 medicinal products and increased hydrocortisone 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.

Cardiovascular risk

Using higher than normal doses of hydrocortisone 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.

General Precautions

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

- a) osteoporosis (postmenopausal females are particularly at risk). All glucocorticoids increase calcium excretion and reduce the bone-remodelling rate. Patients with adrenal insufficiency on long-term glucocorticoid replacement therapy have been found to have reduced bone mineral density;
- b) hypertension or congestive heart failure;
- c) existing or previous history of severe affective disorders (especially previous history of steroid psychosis);
- d) diabetes mellitus (or a family history of diabetes mellitus). Corticosteroids, including hydrocortisone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long term corticosteroid therapy to diabetes mellitus;
- e) previous history of tuberculosis or characteristic appearance on a chest x-ray. The emergence of active tuberculosis can, however, be prevented by the prophylactic use of anti-tuberculous therapy;
- f) 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;
- g) previous corticosteroid-induced myopathy;
- h) liver failure;
- i) renal insufficiency;
- j) epilepsy;
- k) peptic ulceration;
- l) recent myocardial infarction.

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

Thyroid function

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

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

Withdrawal symptoms

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.

Psychiatric effects

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 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.

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.

Lactose intolerance

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

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.

Special populations

Elderly population

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, *see Section 4.2.*

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, retardation, *see Section 4.2.*

4.5. Interaction with other medicines and other forms of interaction

Hydrocortisone interactions listed below have been reported after therapeutic doses of glucocorticoids.

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 medicinal products 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 hydrocortisone.

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 hydrocortisone and thus increase blood levels. During long-term prophylactic treatment with any of the antibiotics, adjustment of the hydrocortisone dosage should be

considered.

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 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 drugs; 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 affects 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. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid states.

Breast-feeding

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 but the benefits of breast feeding are likely to outweigh any theoretical risk.

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 ability to drive and use machines

Patients should be warned about the potential changes in vision and/or muscle weakness, and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known, *see Section 4.8*.

4.8. Undesirable effects

Table 1: Tabulated summary of adverse reactions

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment, *see Section 4.4*.

Adverse events are which have been associated with Hydrocortisone are given below, listed by system organ class and frequency.

Undesirable effects are especially likely to occur at treatment onset or at dose increase.

The undesirable effects are listed below by organ class and the following frequency convention:

Very common: ($\geq 1/10$)

Common: ($\geq 1/100$ to $< 1/10$)

Uncommon: ($\geq 1/1,000$ to $< 1/100$)

Rare: ($\geq 1/10,000$ to $< 1/1,000$)

Very rare: ($< 1/10,000$)

Not known – cannot be estimated from the available data.

The following side effects may be associated with the long-term systemic use of corticosteroids.

System Organ Class	Frequency	Event(s)
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 (<i>see Section 4.4</i>), activation of fungal and viral infections including herpes.
Blood and lymphatic system disorders	Not known	Leucocytosis.
Immune system disorders	Not known	Hypersensitivity including anaphylaxis.
Endocrine disorders	Not known	Suppression of the hypothalamo-pituitary-adrenal axis Growth retardation in infancy, childhood and adolescence Cushingoid facies Induction of glucose intolerance or diabetes mellitus.
Metabolism and nutrition disorders	Not known	Negative protein and calcium balance Sodium and fluid retention Oedema tendency Alkalosis hypokalaemic Hypokalaemia and 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 (<i>see also Section 4.4</i>).
Ear and labyrinth disorders	Not known	Vertigo.
Cardiac Disorders	Not known	Myocardial rupture following recent myocardial infarction.
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 and Nausea.
Skin and subcutaneous tissue disorders	Not known	Impaired healing Skin atrophy Contusion Ecchymosis Skin striae Rash pruritic Cushing-like symptoms Acne Telangiectasia Hirsutism.
Musculoskeletal and connective tissue disorders	Not known	Proximal myopathy Osteoporosis and spontaneous fractures Vertebral and long bone fractures Avascular osteonecrosis Tendon rupture and Joint swelling.
Reproductive system and breast disorders	Not known	Menstruation irregular and amenorrhoea.
General disorders and administration site conditions	Not known	Malaise Fatigue.
Investigations	Not known	Weight increased High density lipoprotein decreased Blood potassium decreased.

- (a) Reactions are common and may occur in both adults and children. In adults, the frequencies of severe reactions have been estimated to be 5-6%. 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 nodules 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. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Symptoms

Overdosage may cause nausea and vomiting, sodium and water retention, hyperglycaemia and occasional gastrointestinal bleeding.

Treatment

Treatment need only be symptomatic although cimetidine by slow intravenous injection or ranitidine by slow intravenous injection may be administered to prevent gastrointestinal bleeding.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids; ATC code: H02AB09

Pharmacodynamic effects

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 11 β HSD 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 6 β -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.

5.3. Preclinical safety data

Animal experiments have shown that prenatal exposure to very high doses of glucocorticoids can induce malformations (cleft palate, skeletal malformations). Animal studies have also shown that prenatal exposure to high doses of glucocorticoids (but lower than teratogenic doses) may be associated with increased risk of intrauterine growth retardation, cardiovascular disease in adulthood and permanent changes in glucocorticoid receptor density, neurotransmitter turnover, and behaviour.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, magnesium stearate, maize starch, povidone, and purified talc.

6.2. Incompatibilities

Not known.

6.3. Shelf life

36 months from date of manufacture.

6.4. Special precautions for storage

Store at or below 30°C and protect from light.

6.5. Nature and contents of container

Available in a plastic bottle containing 100 tablets.

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. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

11 May 1995

10. DATE OF REVISION OF THE TEXT

21 February 2018

Summary table of changes

Section Changed	Summary of new information
4.4	Medsafe request – systemic glucocorticoids and hyperglycaemia