

Summary of Product Characteristics

1. Name of the Medical Product

H2CORT

2. Qualitative & Quantitative Composition:

Hydrocortisone Sodium succinate BP

Equivalent toHydrocortisone 100mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form:

Powder for injection

Visual Description

White amorphous and hygroscopic powder

4. Clinical Particulars

4.1 Therapeutic Indications:

Anti-inflammatory agent.

Hydrocortisone is indicated for any condition in which rapid and intense corticosteroid effect is required such as:

1. Collagen diseases

Systemic lupus erythematosus

2. Dermatological diseases

Severe erythema multiforme (Stevens-Johnson syndrome)

3. Allergic states

Bronchial asthma, anaphylactic reactions

4. Gastro-intestinal diseases

Ulcerative colitis, Crohn's disease

5. Respiratory diseases

Aspiration of gastric contents

4.2 Posology and Method of administration:

Hydrocortisone may be administered by intravenous injection, by intravenous infusion or by intramuscular injection, the preferred method for initial emergency use

being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer-acting injectable preparation or an oral preparation.

Dosage requirements are variable and must be individualized on the basis of the disease under treatment, its severity and the response of the patient over the entire duration of treatment. A risk/benefit decision must be made in each individual case on an ongoing basis.

The lowest possible dose of corticosteroid should be used to control the condition under treatment for the minimum period. The proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage, which will maintain an adequate clinical response, is reached.

Dosage usually ranges from 100 mg to 500 mg depending on the severity of the condition, administered by intravenous injection over a period of one to ten minutes. This dose may be repeated at intervals of 2, 4 or 6 hours as indicated by the patient's response and clinical condition.

In general high-dose corticosteroid therapy should be continued only until the patient's condition has stabilised - usually not beyond 48 to 72 hours. If hydrocortisone therapy must be continued beyond 48 to 72 hours hypernatraemia may occur, therefore it may be preferable to replace Hydrocortisone with a corticosteroid such as methylprednisolone sodium succinate as little or no sodium retention occurs.

Although adverse effects associated with high dose, short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

Patients subjected to severe stress following corticoid therapy should be observed closely for signs and symptoms of adrenocortical insufficiency.

Corticosteroid therapy is an adjunct to, and not a replacement for, conventional therapy.

In patients with liver disease, there may be an increased effect (see section 4.4) and reduced dosing may be considered.

Elderly patients: Hydrocortisone is primarily used in acute short-term conditions. There is no information to suggest that a change in dosage is warranted in the elderly.

However, treatment of elderly patients should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age and close clinical supervision is required (See Section 4.4).

Paediatric population: While the dose may be reduced for infants and children, it is governed more by the severity of the condition and response of the patient than by age or body weight but should not be less than 25 mg daily (see Special warnings and special precautions for use).

Preparation of solutions: For intravenous or intramuscular injection prepare the solution aseptically by adding not more than 2 ml of sterile water for injections to the contents of one vial of Hydrocortisone 100 mg, shake and withdraw for use.

For intravenous infusion, first prepare the solution by adding not more than 2 ml of sterile water for injections to the vial; this solution may then be added to 100 ml 1000 ml (but not less than 100 ml) of 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

If after long-term therapy the drug is to be stopped, it needs to be withdrawn gradually rather than abruptly (see section 4.4).

4.3 Contraindications:

Hydrocortisone is contra-indicated:

- Where there is known hypersensitivity to the active substance or any of the excipients listed in section 6.1
- In systemic fungal infection unless specific anti-infective therapy is employed.
- Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

4.4 Special warnings & precautions for use

Warnings and Precautions:

1. A Patient Information Leaflet is provided in the pack by the manufacturer.
2. Undesirable effects may be minimised by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity (see Section 4.2).
3. Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. In patients who have received more than physiological doses of systemic corticosteroids (approximately 30 mg hydrocortisone) 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 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 3 weeks is appropriate if it considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 160 mg hydrocortisone 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 who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
 - Patients receiving doses of systemic corticosteroid greater than 160 mg hydrocortisone.
 - Patients repeatedly taking doses in the evening.
4. 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, drug, dosage and the duration of treatment.

5. Immunosuppressant Effects/Increased Susceptibility to Infections:

Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non immunosuppressive doses of corticosteroids.

6. Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non immune children or adults on corticosteroids.

Chickenpox is of serious 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 immunization 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.

7. Exposure to measles should be avoided. Medical advice should be sought immediately if exposure occurs. Prophylaxis with normal intramuscular immunoglobulin may be needed.

8. The use of hydrocortisone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease

in conjunction with appropriate antituberculosis regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

9. Allergic reactions may occur. Rarely skin reactions and anaphylactic/anaphylactoid reactions have been reported following parenteral hydrocortisone therapy. Physicians using the drug should be prepared to deal with such a possibility. Appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of drug allergy.

10. Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see section 4.8). 11. Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy monitoring is required. Hydrocortisone may have an increased effect in patients with liver diseases since the metabolism and elimination of hydrocortisone is significantly decreased in these patients.

12. Ocular Effects: Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids. 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. Central serous chorioretinopathy, may lead to retinal detachment.

13. Severe medical events have been reported in association with the intrathecal/epidural routes of administration. There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

14. Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

15. The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short-course, high dose corticosteroids did not support their use. However, meta analyses, and a

review suggest that longer courses (5-11 days) of low dose corticosteroids might reduce mortality, especially in patients with vasopressor dependent septic shock.

16. **Endocrine Effects:** In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic pituitary adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy. In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Drug induced secondary adrenocortical insufficiency may therefore be minimized 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, hormone therapy should be reinstituted. A steroid “withdrawal syndrome,” seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels. Because glucocorticoids can produce or aggravate Cushing’s syndrome, glucocorticoids should be avoided in patients with Cushing’s disease. There is an enhanced effect of corticosteroids on patients with hypothyroidism.

17. **Cardiac Effects:** Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed. Low dose therapy may reduce the incidence of complications in corticosteroid therapy. Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

Special precautions:

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

1. Osteoporosis is generally associated with long term use and large doses of glucocorticoids. Corticosteroids should be used with caution in patients with osteoporosis (post-menopausal females are particularly at risk).
2. Hypertension.

3. Existing or previous history of severe affective disorders (especially previous steroid psychosis).
4. Corticosteroids, including hydrocortisone, can increase blood glucose, worsen pre existing diabetes, and predispose those on long term corticosteroid therapy to diabetes mellitus (or a family history of diabetes).
5. History of tuberculosis.
6. Glaucoma (or a family history of glaucoma).
7. Previous corticosteroid-induced myopathy.
8. Liver failure or cirrhosis.
9. Corticosteroids should be used with caution in patients with renal insufficiency.
10. Epilepsy.
11. Peptic ulceration.
12. Fresh intestinal anastomoses.
13. Predisposition to thrombophlebitis.
14. Abscess or other pyogenic infections.
15. Ulcerative colitis.
16. Diverticulitis.
17. Myasthenia gravis.
18. Recent myocardial infarction (myocardial rupture has been reported).
19. Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.
20. Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.
21. Investigations: Hydrocortisone can cause elevation of blood pressure, salt and water retention and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.\
22. 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 treatment. Risks may be higher with high doses/systemic exposure (see section 4.5) that can increase the risk of side effects), 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 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.

23. Gastrointestinal effect: High doses of corticosteroids may produce acute pancreatitis. There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with nonsteroidal antiinflammatory drugs (NSAIDs), the risk of developing gastrointestinal ulcers is increased.

24. Other: Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment as to whether daily or intermittent therapy should be used.

The lowest possible dose of corticosteroid should be used to control the condition under treatment and when reduction in dosage is possible, the reduction should be gradual.

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 (see section 4.5).

Aspirin and nonsteroidal anti inflammatory agents should be used cautiously in conjunction with corticosteroids (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Corticosteroids should be used with caution in patients with seizure disorders.

Paediatric population: Corticosteroids cause growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. The use of steroids should be restricted to the most serious indications.

Use in the elderly: 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. Systemic corticosteroids are not indicated for, and therefore should not be used to treat traumatic brain injury or stroke because it is unlikely to be of benefit and may even be harmful. For traumatic brain injury a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A casual association with methylprednisolone sodium succinate treatment has not been established.

4.5 Interactions with other medicinal products and other forms of Interactions Contraindicated combinations

1. Hydrocortisone is metabolized by 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) and the cytochrome P450 (CYP) 3A4 enzyme. The CYP3A4 enzyme catalyzes 6 β -hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.
2. CYP3A4 INHIBITORS - May decrease hepatic clearance and increase the plasma concentrations of hydrocortisone. In the presence of a CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, and grapefruit juice), the dose of hydrocortisone may need to be decreased to avoid steroid toxicity.
3. CYP3A4 INDUCERS - May increase hepatic clearance and decrease the plasma concentrations of hydrocortisone. In the presence of a CYP3A4 inducer (e.g., rifampin, carbamazepine, phenobarbital, and phenytoin), the dose of hydrocortisone may need to be increased to achieve the desired response.
4. CYP3A4 SUBSTRATES - In the presence of another CYP3A4 substrate, the hepatic clearance of hydrocortisone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration.
5. NON-CYP3A4-MEDIATED EFFECTS - Other interactions and effects that occur with hydrocortisone are described in Table 1 below. Table 1 provides a list and descriptions of the most common and/or clinically important drug interactions or effects with hydrocortisone.

Table 1. Important drug or substance interactions/ effects with hydrocortisone

Drug Class or Type - DRUG or SUBSTANCE	Interaction/Effect
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Antibacterial - ISONIAZID	CYP3A4 INHIBITOR
Antibiotic, Antitubercular - RIFAMPIN	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants	CYP3A4 INDUCERS

- PHENOBARBITAL - PHENYTOIN	
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see section 4.4 Special warnings and precautions for use, Musculoskeletal Effects, for additional information). 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungals - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES)

Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Pharmacokinetic enhancers - COBICISTAT	CYP3A4 INHIBITORS
Aromatase Inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Cardiac Glycosides - DIGOXIN	Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalemia. In all patients taking any of these drug therapy combinations, serum electrolyte

	determinations, particularly potassium levels, should be monitored closely.
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE)
Oestrogens (including oral contraceptives containing oestrogens)	CYP3A4 INHIBITOR (and SUBSTRATE) Oestrogens may potentiate effects of hydrocortisone by increasing the concentration of transcortin and thus decreasing the amount of hydrocortisone available to be metabolized. Dosage adjustments of hydrocortisone may be required if oestrogens are added to or withdrawn from a stable dosage regimen.
GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
Immunosuppressant - CICLOSPORIN	CYP3A4 INHIBITOR (and SUBSTRATE) Increased activity of both ciclosporin and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide Antibacterial CLARITHROMYCIN ERYTHROMYCIN	CYP3A4 INHIBITOR (and SUBSTRATES)

Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR
NSAIDs - high-dose ASPIRIN (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Corticosteroids may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of corticosteroid treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.
Potassium Depleting Agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalemia. There is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and
	congestive heart failure.

4.6 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 effects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate in man, however, when administered for long 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 usually resolves 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 state. Some corticosteroids readily cross the placenta. Some retrospective studies have found an increased incidence of low-birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

Breast-feeding

Corticosteroids are excreted in breast milk, although no data are available for hydrocortisone. Doses up to 160 mg daily of hydrocortisone 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 breastfeeding are likely to outweigh any theoretical risk.

This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

Fertility

Corticosteroids have been shown to impair fertility in animal studies. Adverse effects on fertility in rats with corticosterone were observed in males only and were reversible (see section 5.3). The clinical relevance of this information is uncertain.

4.7 Effects on ability to drive and use machine*:

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as syncope, vertigo, and convulsions are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

4.8 Undesirable Effects*:

Since hydrocortisone is normally employed on a short-term basis it is unlikely that side effects will occur; however, the possibility of side effects attributable to corticosteroid therapy should be recognised (see section 4.4). Such side effects include:

System Organ Class	Frequency Not Known (Cannot be estimated from available data)
Infections and infestations	Opportunistic infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Kaposi's sarcoma (has been reported to occur in patients receiving corticosteroid therapy)
Blood and lymphatic system disorders	Leucocytosis
Immune system disorders	Drug hypersensitivity; Anaphylactic reaction; Anaphylactoid reaction

Endocrine disorders	Cushingoid; Hypothalamic pituitary adrenal axis suppression; Steroid withdrawal syndrome; Steroid withdrawal syndrome WITHDRAWAL SYMPTOMS - Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see section 4.4); A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight
Metabolism and nutrition disorders	Metabolic acidosis; Sodium retention; Water retention; Alkalosis hypokalaemic; Dyslipidaemia; Glucose tolerance impaired; Increased insulin requirement (or oral hypoglycemic agents in diabetics); Lipomatosis; Increased appetite; Weight increased
Psychiatric disorders	Affective disorders (including Depression, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation); Psychotic disorder (including Mania, Delusion, Hallucination, and aggravation of Schizophrenia); Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behaviour; Insomnia; Irritability.
Nervous system disorders	Epidural lipomatosis; Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of hydrocortisone; Benign intracranial hypertension; Seizure; Amnesia; Cognitive disorder; Dizziness; Headache.
Eye disorders	Central serous chorioretinopathy ; Cataract; Glaucoma; Exophthalmos; Vision blurred (see also section 4.4); Increased intra-ocular pressure, with possible damage to the optic nerve; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease;
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Cardiac failure congestive (in susceptible patients); Myocardial rupture following a myocardial infarction; Hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders	Thrombosis including Thromboembolism; Hypertension; Hypotension
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism; Hiccups

Gastrointestinal disorders	Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage); Intestinal perforation; Gastric haemorrhage; Pancreatitis; Oesophageal ulceration; Oesophageal candidiasis; Abdominal distension; Abdominal pain; Diarrhoea; Dyspepsia; Nausea
Skin and subcutaneous tissue disorders	Angioedema; Hirsutism; Petechiae; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Skin striae; Rash; Pruritus; Urticaria; Acne; Skin hypopigmentation; Telangiectasia; Skin hyperpigmentation;
Musculoskeletal and connective tissue disorders	Muscular weakness; Myalgia; Myopathy; Muscle atrophy; Osteoporosis Osteonecrosis; Pathological fracture; Neuropathic arthropathy; Arthralgia; Growth retardation
Reproductive system and breast disorders	Menstruation irregular; Amenorrhoea
General disorders and administration site conditions	Impaired healing; Oedema peripheral; Fatigue Abscess sterile; Malaise; Injection site reaction
Investigations increased	Carbohydrate tolerance decreased; Blood potassium decreased; Urine calcium increased; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood alkaline phosphatase increased; Blood urea increased; Suppression of reactions to skin tests*; Weight
Injury, poisoning and procedural complications	Spinal compression fracture; Tendon rupture (particularly of the Achilles tendon)

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

4.9 Overdose:

There is no clinical syndrome of acute overdosage with corticosteroids. Hydrocortisone is dialysable. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

5. Pharmacological properties:

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Glucocorticoids

ATC code: H02AB09

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The highly water-soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly

useful where high blood levels of hydrocortisone are required rapidly. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is five to one. This is consistent with the relative oral potency of methylprednisolone and hydrocortisone.

5.2 Pharmacokinetics Properties*:

The pharmacokinetics of hydrocortisone in healthy male subjects demonstrated nonlinear kinetics when a single intravenous dose of hydrocortisone sodium succinate higher than 20 mg was administered, and the corresponding pharmacokinetic parameters of hydrocortisone are presented in Table 2

Table 2. Mean (SD) hydrocortisone pharmacokinetic parameters following single intravenous doses

	Healthy Male Adults (21-29 years; N = 6)			
Dose (mg)	5	10	20	40
Total Exposure (AUC _{0-∞} ; ng·h/mL)	410 (80)	790 (100)	1480 (310)	2290 (260)
Clearance (CL; mL/min/m ²)	209 (42)	218 (23)	239 (44)	294 (34)
Volume of Distribution at Steady State (V _{dss} ; L)	20.7 (7.3)	20.8 (4.3)	26.0 (4.1)	37.5 (5.8)
Elimination Half-life (t _{1/2} ; hr)	1.3 (0.3)	1.3 (0.2)	1.7 (0.2)	1.9 (0.1)

AUC_{0-∞} = Area under the curve from time zero to infinity.

Absorption

Following administration of 5, 10, 20, and 40 mg single intravenous doses of hydrocortisone sodium succinate in healthy male subjects, mean peak values obtained at 10 minutes after dosing were 312, 573, 1095, and 1854 ng/mL,

respectively. Hydrocortisone sodium succinate is rapidly absorbed when administered intramuscularly.

Distribution

Hydrocortisone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. The volume of distribution at steady state for hydrocortisone ranged from approximately 20 to 40 L (Table 2). Hydrocortisone binds to the glycoprotein transcortin (i.e., corticosteroid binding globulin) and albumin. The plasma protein binding of hydrocortisone in humans is approximately 92%.

Biotransformation

Hydrocortisone (i.e., cortisol) is metabolized by 11 β -HSD2 to cortisone, and further to dihydrocortisone and tetrahydrocortisone. Other metabolites include dihydrocortisol, 5 α -dihydrocortisol, tetrahydrocortisol, and 5 α -tetrahydrocortisol. Cortisone can be converted to cortisol through 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1). Hydrocortisone is also metabolized by CYP3A4 to 6 β -hydroxycortisol (6 β -OHF), and 6 β -OHF varied from 2.8% to 31.7% of the total metabolites produced, demonstrating large inter-individual variability.

Elimination

Excretion of the administered dose is nearly complete within 12 hours. When hydrocortisone sodium succinate is administered intramuscularly, it is excreted in a pattern similar to that observed after intravenous injection.

5.3 Preclinical safety data

Carcinogenesis:

Hydrocortisone did not increase tumor incidences in male and female rats during a 2year carcinogenicity study.

Mutagenesis:

Corticosteroids, a class of steroid hormones that includes hydrocortisone, are consistently negative in the bacterial mutagenicity assay. Hydrocortisone and dexamethasone induced chromosome aberrations in human lymphocytes in vitro and in mice in vivo. However, the biological relevance of these findings is not clear since hydrocortisone did not increase tumor incidences in male and female rats during a 2year carcinogenicity study. Fludrocortisone (9 α -fluorohydrocortisone, structurally similar to hydrocortisone) was negative in the human lymphocyte chromosome aberration assay.

Reproductive toxicity:

Corticosteroids have been shown to reduce fertility when administered to rats. Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live fetuses were reduced. Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), and intra-uterine growth

retardation. With hydrocortisone, cleft palate was observed when administered to pregnant mice and hamsters during organogenesis.

6. Pharmaceutical particulars:

6.1 List of Excipients:

none

6.2 Incompatibilities:

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life:

36 months

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C and 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special Precautions for storage:

This medicinal product does not require any special temperature conditions. Keep the vial in the outer carton to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container:

7.5 ml clear USP Type-III glass vials, grey butyl rubber plugs & sealed with aluminium seals.

6.6 Special precautions for disposal:

NA

7. Marketing Authorization Holder:

Samrudh Pharmaceuticals Ltd.

100000000000251

India

Manufacturing Site Address:

Samrudh Pharmaceuticals Ltd.

100000000000251

India

8. Marketing Authorization Numbers:

H2024/CTD9333/19837

9. Date of first registration /renewal of the registration:

2024 March 25

10. Date of revision of text:

2024 March 25