

Summary of Product Characteristics

1. Name of the Medicinal Product

Hydracort, Hydrocortisone Sodium Succinate eq. to Hydrocortisone 100 mg, Powder for solution for injection/infusion

2. Quality and Quantitative Composition

Each vial contains Hydrocortisone Sodium Succinate eq. to Hydrocortisone 100 mg.

3. Pharmaceutical Form: White to off-white sterile powder.

4. Clinical Particulars

4.1 Therapeutic indication:

When oral therapy is not feasible, and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the intravenous or intramuscular use of Hydracort sterile powder is indicated as follows:

Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reaction, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal disease: To tide the patient over a critical period of the disease in regional enteritis (systemic therapy) and ulcerative colitis.

Hematologic disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond Blackfan anemia), idiopathic thrombocytopenic purpura in adults (intravenous administration only; intramuscular administration is contraindicated), pure red cell aplasia, select cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Neoplastic disease: For the palliative management of leukemias and lymphomas.

Nervous System: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor, or craniotomy

Ophthalmic diseases: Sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome, of that due to lupus erythematosus.

Respiratory diseases: Berylliosis, fulmination or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), For the treatment of dermatomyositis, temporal arteritis, polymyositis, and systemic lupus erythematosus.

4.2 Posology and method of administration:

Because of possible physical incompatibilities, should not be diluted or mixed with other solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The preparation 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 action injectable preparation or and oral preparation.

Therapy is initiated by administering intravenously over a period of 30 seconds (e.g., 100 mg) to 10 minutes (e.g., 500 mg or more). In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized, usually not beyond 48 to 72 hours. When high dose hydrocortisone therapy must be continued beyond 48-72 hours, hypernatremia may occur. Under such circumstances, it may be desirable to replace hydrocortisone with a corticoid such as methylprednisolone sodium succinate which causes little or no sodium retention.

The initial dose is 100 mg to 500 mg, depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages may be justified and may be in multiples of the oral dosages.

The dose may be repeated at intervals of 2, 4, or 6 hours as indicated by the patient's response and clinical condition.

It Should Be Emphasized that Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the response of the Patient. After a favorable response is noted. The proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate

time intervals until the lowest dosage that maintains an adequate clinical response is reached. Situations that may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation, it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. It after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 800 mg of hydrocortisone for a week followed by 320 mg every other day for one month are recommended. (See **Special warning and precautions for use, Neurologic-psychiatric**)

In pediatric patients, the initial dose of hydrocortisone may vary depending on the specific disease entity being treated. The range of initial dose is 0.56 to 8 mg/kg/day in three or four divided doses (20 to 240 mg/m²bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

Cortisone, 25	Prednisone, 5	Paramethasone, 2
Hydrocortisone, 20	Methylprednisolone, 4	Betamethasone, 0.75
Prednisolone, 5	Triamcinolone, 4	Dexamethasone, 0.75

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

Preparation of Solutions:

100 mg Plain-For intravenous or intramuscular injection, prepare solution by aseptically adding **not more than 2 mL** of Bacteriostatic Water for Injection or Bacteriostatic Sodium Chloride Injection or Sterile water for injection to the contents of one vial.

For intravenous infusion, First prepare solution by adding **not more than 2 mL** of Bacteriostatic Water for Injection or Bacteriostatic Sodium Chloride Injection or Sterile water for injection to the vial; this solution may then be added to 100 to 1000 mL of the following: 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

4.3 Contraindications

Hydrocortisone is contraindicated:

- in patients where there is known hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- in patients who have 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 warning and precautions for use

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration:

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General:

Injection of Hydrocortisone sodium succinate may result in dermal and/or subdermal changes forming depressions in the skin at the injection site. In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **Undesirable effects**).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Cardio-renal:

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased 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.

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.

Endocrine:

Hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use. Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may 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 reinstated.

Infections

General: Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents.

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infections complications increases. Corticosteroids may also mask some signs of current infection. Do not use intra-articularly, intrabursally, or for intratendinous administration for *local* effect in the effect in the presence of acute local infection.

Fungal infections: Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **Contraindication and Interaction with other medicinal products and other forms of interactions**, Amphotericin B injection and potassium-depleting agents).

Special pathogens: Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, and *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis: The use of corticosteroids 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 an appropriate antituberculous 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.

Viral infections: Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these disease, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the

risk is not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic:

Reports of severe medical events have been associated with the intrathecal route of administration (see

Undesirable effects, Neurologic/Psychiatric)

Ophthalmic:

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 bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes.

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

Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General:

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

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 and as to whether daily or intermittent therapy should be used.

Cardio-renal:

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine:

Drug-induced secondary adrenocortical insufficiency may 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 reinstated. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increase in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Gastrointestinal:

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific ulcerative colitis, since they may increase the risk of a perforation. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Musculoskeletal:

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Local injection of a steroid into a previously infected site is not usually recommended.

Neurologic-psychiatric:

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **Posology and method of administration**).

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic:

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Other:

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. In patients with suspected pheochromocytoma, consider the risk of pheochromocytoma crisis prior to administering corticosteroids.

Information for Patients:

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

4.5 Interaction with other medicinal products and other forms of interactions

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (e.g., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiation corticosteroids therapy.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentration, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin): Drugs that induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin):

Drugs that inhibit cytochrome P450 3A4 have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole: Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroids side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin test: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroids therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS: Infections, Vaccination**).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Corticosteroids have been shown to impair fertility in male rats.

4.6 Pregnancy and lactation

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers:

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions infants from corticosteroids, a decision should be made whether to continue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric for the treatment of nephrotic syndrome (>2 years of age) and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids (e.g., severe asthma and wheezing) are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations. The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **Undesirable effects**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Geriatric Use:

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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

Allergic reaction: Allergic or hypersensitivity reactions, anaphylactoid reaction, anaphylaxis, angioedema.

Blood and lymphatic system disorders: Leukocytosis.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, burning or tingling (especially in the perineal area, after intravenous injection), cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increase sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increase appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo, Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see **WARNINGS: Neurologic**), epidural lipomatosis.

Ophthalmic: Central serous chorioretinopathy, exophthalmoses, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see **WARNINGS**), malaise, moon face, weight gain.

4.9 Overdose

Treatment of acute overdose is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

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-inflammation 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 Pharmacokinetic 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 below Table

Mean (SD) hydrocortisone pharmacokinetic parameters following single intravenous doses

Dose (mg)	Healthy Male Adults (21-29 years; N=6)			
	5	10	20	40
Total Exposure ($AUC_{0,\infty}$; 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)

$AUC_{0,\infty}$ = 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 (above table). Hydrocortisone binds to the glycoprotein transcortin (i.e., corticosteroid binding globulin) and albumin. The plasma protein binding of hydrocortisone in humans is approximately 92%.

Metabolism: 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.

Excretion: 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 tumour incidences in male and female rats during a 2-year 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 tumour incidences in male and female rats during a 2-year 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: -

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

The chemical and physical in-use stability of reconstituted with 2 ml Bacteriostatic Water for Injection or Bacteriostatic Sodium Chloride Injection in the vial, has been demonstrated for 72 hours in refrigerator (2-8°C) or store below 30°C.

The chemical and physical in-use stability of reconstituted with 2 ml Sterile water for injection, has been demonstrated for 24 hours in refrigerator (2-8°C) or store below 30°C.

The chemical and physical in-use stability of dilution with 5% dextrose in water or isotonic saline solution or 5% dextrose in isotonic saline solution, has been demonstrated for 24 hours in refrigerator (2-8°C) or store below 30°C.

6.4 Special precautions for storage

Store below 30° C

See section 6.3. No diluents other than those referred to are recommended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

6.5 Nature and contents of container

Clear glass vial (Type I) with grey chlorobutyl rubber stopper, sealed with aluminium/polypropylene flip-off cap contains Hydrocortisone sodium succinate eq. to hydrocortisone 100 mg, packed or unpacked in a box of 1, 5, 10, 20, 25, 50 and 100 vials.

6.6 Special precaution for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

ABLE MEDICAL COMPANY LIMITED

111 Moo. 9 Nong Son, Chiang Yuen,

Maharakham 44160, Thailand

8. Marketing Authorization Numbers

1A 15201/63

9. Date of authorization

17 December, 2020

10. Date of revision of the text

6 June, 2023