SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydrocortison Medochemie 100 mg poeder voor oplossing voor injectie/infusie

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 133.7 mg hydrocortisone sodium succinate, equivalent to 100 mg hydrocortisone.

Excipient with known effect: sodium.
Each vial contains 7.65 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion
White or nearly white, hygroscopic amorphous powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution treatment in primary adrenocortical insufficiency (Addison's disease and adrenogenital syndrome) and secondary (due to (pan)hypopituitarism) adrenocortical insufficiency. In the first case it should be combined with a mineralocorticoid.

Hydrocortisone is indicated for any condition in which rapid and intense corticosteroid effect is required such as:
- in case of severe exacerbations of chronic lung disease (asthma, bronchitis, and emphysema).
- in status asthmaticus.
- as an adjuvant in severe anaphylactic reactions.

4.2 Posology and method of administration

Posology
Hydrocortisone can be administered by intravenous or intramuscular injection or intravenous infusion. Intravenous injection is the most commonly chosen method for initial treatment of emergencies. After this initial period, a longer-acting injectable or oral preparation should be considered. The duration of intravenous administration depends on the dose; it can vary from 30 seconds (e.g. 100 mg) to 10 minutes (e.g. 500 mg or more).

Dosage requirements are variable and should be determined individually based on the disease being treated, its severity, and the patient's response throughout the duration of treatment. A risk/benefit decision must be made on an ongoing basis for each individual patient.

Where possible, the use of corticosteroids should be limited to the lowest possible dose for a minimum period of time. The appropriate maintenance dosage should be determined by reducing the initial dose of the medicine in small amounts at appropriate time intervals until the lowest dosage that will maintain an adequate clinical response is reached.

In general, high-dose glucocorticoid therapy should only be continued until the patient's condition has stabilized (usually not longer than 48 to 72 hours).
Although short-term treatments with high doses of glucocorticoids are sometimes associated with undesirable effects, gastric ulceration may occur. Prophylactic use of antacids may be indicated.

If treatment with high doses of hydrocortisone has to be continued for longer than 48 to 72 hours, hypernatremia may occur. In that case, it may be desirable to replace hydrocortisone with a glucocorticoid preparation such as methylprednisolone sodium succinate, which causes little or no sodium retention.

If the medicine is to be discontinued after long-term therapy, it should be discontinued gradually rather than abruptly (see section 4.4).

The initial dose of hydrocortisone is 100 mg to 500 mg or more depending on the severity of the condition. This dose may be repeated at intervals of 2, 4 or 6 hours as required by the patient's clinical condition. Glucocorticoid therapy is intended to support, not replace, conventional treatment.

Hydrocortisone may have an enhanced effect in patients with liver disease as the metabolism and elimination of hydrocortisone is significantly reduced in these patients. A dose reduction should be considered.

Paediatric population
The dosage of hydrocortisone in paediatric population is determined by the severity of the condition and the patient's response rather than by age or body weight. It may be reduced for these patients, but should never be less than 25 mg per day.

Method of administration
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.
This medicine is not recommended for use by the intrathecal or epidural route of administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Acute infectious processes: viral infections and systemic fungal infections (bacterial infections: see section 4.4).
Ulcers peptic and duodenal.
Tropical worm infections.
Vaccination with live or attenuated virus with immunosuppressive doses of glucocorticoids (See also section 4.4).
Epidural administration.
The general contraindications and precautions for the use of systemic glucocorticoid therapy also apply to hydrocortisone.

4.4 Special warnings and precautions for use

Severe clinical events (including arachnoiditis, meningitis, paraplegia, and cauda equina syndrome) have been reported in association with the intrathecal route of administration. Therefore the risk of an intrathecal administration should only be considered in case other routes of administration are not possible.

General
Because complications of treatment with glucocorticoids depend on the dose and duration of treatment, a risk-benefit assessment must be made in each individual case with regard to dosage and duration of treatment, and whether daily or intermittent administration should be used.
The lowest possible dose of corticosteroid should be used to control the condition being treated. A gradual reduction in dosage should be used as soon as possible.

Aspirin and non-steroidal anti-inflammatory medicines should be used with caution when co-administered with corticosteroids (see section 4.5).

Immunosuppressive effects/increased susceptibility to infections

Glucocorticoids can increase susceptibility to infections, can mask certain symptoms of an infection and during their use new infections can develop. In the case of bacterial infections, the causative agent(s) should first be determined if possible. After this, the infection should be treated before starting glucocorticoid administration. Under the influence of glucocorticoids, resistance may decrease and localization of the infection may be difficult.

Infections with all types of pathogens, including viruses, bacteria, fungi, protozoa and helminths, may be associated with the use of glucocorticoids as monotherapy, but also in combination with other immunosuppressive agents that affect cellular and humoral immunity and neutrophil function. These infections can be mild, but sometimes serious or even fatal. Infectious complications occur more frequently with higher doses of glucocorticoids.

Vaccination with live or attenuated viruses is contraindicated in patients receiving immunosuppressive doses of glucocorticoids. Killed or inactivated vaccines may be administered to these patients, although response may be reduced. Vaccination with live or attenuated viruses is not contraindicated in patients receiving non-immunosuppressive doses of glucocorticoids.

The use of hydrocortisone sodium succinate in active tuberculosis should be limited to cases of fulminating or disseminated tuberculosis, where the glucocorticoid is administered in combination with an adequate tuberculosis agent.

Patients with latent tuberculosis or tuberculin reactivity should be closely monitored during corticotherapy to detect possible reactivation of the disease in a timely manner. During long-term glucocorticoid therapies, these patients should receive chemoprophylactic treatment.

The occurrence of Kaposi's sarcoma has been reported in patients receiving glucocorticoid therapy. Discontinuation of therapy may lead to clinical remission.

Publications regarding the use of corticosteroids in septic shock show both beneficial and adverse effects. Routine use in septic shock is not recommended. Nevertheless, recent studies suggest that adjunctive corticosteroid therapy may provide benefit in patients with septic shock suffering from adrenal insufficiency. In particular, longer administration (5-11 days) of low-dose corticosteroids could reduce mortality, especially in patients with vasopressor-dependent septic shock.

Effects on immune system

Allergic reactions may occur. Since some rare cases of skin reactions and anaphylactic/anaphylactoid reactions (e.g. bronchospasm) have occurred in patients treated with parenteral glucocorticoids, appropriate precautions should be taken before administering the medicine, especially if the patient has had a previous allergic reaction to a medicine.

Endocrine effects

In patients who are exposed to unusual stress during glucocorticoid therapy (surgery, trauma, infection), an increased dose of fast-acting glucocorticoids should be prescribed before, during and after this stress condition. Patients exposed to severe stress after glucocorticoid therapy should be monitored very carefully for symptoms of adrenal insufficiency.

Long-term administration of pharmacological doses of corticosteroids may result in suppression of the hypothalamic-pituitary-adrenal axis, or HPA axis (secondary adrenocortical insufficiency). The degree and duration of this adrenocortical insufficiency varies per patient and depends on dose, frequency, time of administration and duration of glucocorticoid treatment. In patients with secondary adrenal insufficiency, acute adrenal insufficiency (Addison's crisis) may occur with a possibly fatal outcome if glucocorticoid treatment is abruptly stopped. In these patients, treatment should be discontinued by means of a gradual dose reduction. This type of relative insufficiency may persist for months after treatment ends. In any stressful situation during this period, hormone therapy should be restarted.

A steroid withdrawal syndrome, in which possible adrenal insufficiency does not appear to play a role, can also occur after sudden discontinuation of glucocorticoid therapy. The symptoms of this syndrome include: anorexia, nausea, vomiting, lethargy, headache, fever, arthralgia, skin peeling, myalgia, weight loss and/or hypotension.

Glucocorticoids can cause or worsen Cushing's syndrome and therefore glucocorticoids should be avoided in patients with Cushing's disease.

Corticosteroids have an enhanced effect in patients with hypothyroidism. In patients with hyper- or hypothyroidism, thyroid hormone replacement therapy should be monitored during corticosteroid treatment.

Thyrotoxic Periodic Paralysis (TPP) can occur in patients with hyperthyroidism and with hydrocortisone-induced hypokalaemia. TPP must be suspected in patients treated with hydrocortisone presenting signs or symptoms of muscle weakness, especially in patients with hyperthyroidism.
If TPP is suspected, levels of blood potassium must be immediately monitored and adequately managed to ensure the restoration of normal levels of blood potassium.

Nutrition and metabolism
Corticosteroids, including hydrocortisone, may increase blood glucose, aggravate pre-existing diabetes and increase the risk of diabetes mellitus in patients on long-term corticosteroid treatment.

Psychological effects
During glucocorticoid therapy, psychological disorders may occur, ranging from euphoria, insomnia, unstable mood, altered personality and severe depression to unmistakable psychotic symptoms. Existing emotional instability and psychotic tendencies can also be exacerbated by glucocorticoids.
The use of systemic steroids can potentially cause serious psychological side effects. Symptoms usually occur within a few days or weeks of starting treatment. Most side effects disappear after dose reduction or discontinuation, however specific treatment may be necessary.
Psychological effects have been reported after discontinuation of corticosteroid therapy, the frequency is unknown. Patients/caregivers should be encouraged to seek medical care if psychological symptoms develop in the patient, especially if depression or suicidal thoughts are suspected. Patients/caregivers should be aware of possible psychiatric disorders that may occur during or immediately after dose reduction/discontinuation of systemic steroid treatment.

Effects on the nervous system
Corticosteroids should be used cautiously in patients with seizure disorders.
Corticosteroids should be used with caution in patients with myasthenia gravis (see also myopathy in *Effects on the musculoskeletal system* section).
Serious medical events have been reported in association with the intrathecal/epidural routes of administration (see section 4.8).
Epidural lipomatosis has been reported in patients taking corticosteroids, usually with long-term use in high doses.

Ocular effects
Due to the risk of corneal perforation, glucocorticoids should be used with caution in the case of herpes simplex ocularis. Regular ophthalmological check-ups are highly desirable.
Long-term use of corticosteroids can cause posterior subcapsular cataract, as well as nuclear cataract (especially in children), exophthalmos or increased intraocular pressure, which can lead to glaucoma with possible damage to the optic nerves. The development of secondary fungal and viral infections of the eye may also be increased in patients receiving glucocorticoids.
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient develops symptoms such as blurred vision or other visual disturbances, consideration should be given to referring the patient to an ophthalmologist for evaluation of possible causes including cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) that have been reported following use of systemic and topical corticosteroids. Central serous chorioretinopathy can lead to retinal detachment.

Effects on the heart
Due to side effects of corticoids on the cardiovascular system, such as dyslipidaemia and hypertension, treated patients with existing cardiovascular risk factors are at increased risk of additional cardiovascular side effects in case of high doses and long-term use. Additional checks for at-risk patients are recommended.
Systemic corticosteroids should be used cautiously and only when clearly necessary in congestive heart failure.

Effects on blood vessels
Thrombosis, including venous thromboembolism, has been reported with the use of corticosteroids (see section 4.8). Corticosteroids should therefore be used with caution in patients with or predisposed to thromboembolic disorders.
Steroids should be used with caution in patients with hypertension.

Effects on the gastrointestinal tract
High doses of corticosteroids can cause acute pancreatitis.
Glucocorticoid therapy can mask the symptoms of a (peptic) ulcer, causing perforations or bleeding to occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs/symptoms related to gastrointestinal disorders, such as perforation, obstruction or pancreatitis. In combination with non-steroidal anti-inflammatory medicines (NSAIDs), the risk of developing gastrointestinal ulcers is increased.
In non-specific ulcerative colitis, glucocorticoids should be used with caution if there is a possibility of impending perforation, abscess or other pyogenic infection. Caution is also advised in case of diverticulitis, recent intestinal anastomosis or active or latent peptic ulcer.

Effects on liver
Hydrocortisone may have an enhanced effect in patients with liver disease as the metabolism and elimination of hydrocortisone is significantly reduced in these patients. A dose reduction should be considered.

Effects on the musculoskeletal system
Acute myopathy has been described with the use of high doses of glucocorticoids, usually in patients with disorders of neuromuscular transmission (e.g. myasthenia gravis) or in patients receiving concomitant treatment with anticholinergic medicines such as neuromuscular blockers (e.g. pancuronium). This is a generalized myopathy that may involve eye and respiratory muscles and may result in quadriparesis. Increase in creatine kinase concentration may occur. Improvement or recovery of the clinical picture may take weeks to years after discontinuation of glucocorticoids.
Osteoporosis is a common but rarely recognized side effect related to long-term use of high doses of glucocorticoids.

Kidney and urinary tract disorders
Corticosteroids should be used with caution in patients with renal impairment.

Investigations
Caution should be exercised when administering hydrocortisone to patients with congestive heart failure due to the mineralocorticoid effect of hydrocortisone.
Hydrocortisone can cause an increase in blood pressure, water and salt retention and increased potassium excretion. A sodium-free diet and potassium supplementation may be necessary. All glucocorticoids increase calcium excretion.

Injuries, poisoning and procedural complications
A multicenter study demonstrated increased mortality at 2 weeks and 6 months after injury in patients treated with methylprednisolone sodium succinate compared to placebo. Systemic corticosteroids are not indicated and therefore should not be administered for the treatment of traumatic brain injury. A causal relationship with treatment with methylprednisolone sodium succinate has not been established.

Other
Concomitant treatment with CYP3A inhibitors, including medicinal products containing cobicistat, is expected to increase the risk of systemic adverse reactions. The combination should be avoided unless the benefits outweigh the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects.
Pheochromocytoma crisis, which may be fatal, has been reported following administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after adequate evaluation of the risks and benefits.

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

Paediatric population
Growth inhibition may occur in children who are treated with glucocorticoids in divided daily doses for a long time. This schedule is only justified for very serious indications.
To prevent growth inhibition, children, even more so than adults, should strive for a varied dosage. The growth and development of infants/preschoolers and children receiving long-term corticosteroid therapy should be closely monitored.
Infants and children treated with corticosteroids for a long time are at increased risk of increased intracranial pressure.
High doses of corticosteroids can cause pancreatitis in children.
Hypertrophic cardiomyopathy has been reported following administration of hydrocortisone to preterm infants. Therefore, appropriate diagnostic assessment and monitoring of cardiac function and structure should be performed.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Hydrocortisone is metabolized by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and the enzyme 3A4 of cytochrome P450 (CYP) (see section 5.2).

CYP3A4 INHIBITORS – may decrease hepatic clearance and increase plasma concentrations of hydrocortisone. When co-administered with a CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin and grapefruit juice), it may be necessary to reduce the dose of hydrocortisone to avoid steroid toxicity.

CYP3A4 INDUCTORS – may increase hepatic clearance and decrease plasma concentrations of hydrocortisone. When co-administered with a CYP3A4 inducer (e.g. rifampin, carbamazepine, phenobarbital and phenytoin), it may be necessary to increase the dose of hydrocortisone to achieve the desired result.

CYP3A4 SUBSTRATES – Co-administration of another CYP3A4 substrate may affect the hepatic clearance of hydrocortisone, resulting in appropriate dose adjustment. Side effects of each individual medicine may be more likely to occur when administered simultaneously.

NON-CYP3A4 ADVERSE EFFECTS – Other interactions and adverse reactions occurring with hydrocortisone are described in Table 1 below.
Table 1 lists the most common and/or clinically important interactions or adverse reactions with hydrocortisone.

Table 1. Important interactions/side effects of medicines or substances with hydrocortisone

Medicine class or type *- Medicine or substance*	*Interaction/Side Effect*
Antibacterial - Isoniazid	CYP3A4 INHIBITOR
Antibiotics, Anti-Tuberculosis - Rifampin	CYP3A4-INDUCTOR
Anticoagulants (oral)	The influence of corticosteroids on oral anticoagulants varies. Both increased and decreased anticoagulant activity has been reported when

Medicine class or type *- Medicine or substance*	*Interaction/Side Effect*
	used concomitantly with corticosteroids. For a good anticoagulant effect, it is therefore necessary that the degree of coagulation is always properly monitored.
Anticonvulsants - Carbamazepine	CYP3A4 INDUCTOR (and SUBSTRATE)
Anticonvulsants - Phenobarbital - Phenytoin	CYP3A4 INDUCTORS
Anticholinergics - Neuromuscular Blockers	Corticosteroids may influence the action of anticholinergics. 1) Acute myopathy has been reported with concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking agents (for further information see section 4.4). 2) An antagonistic effect of the neuromuscular blocking action of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may occur with all competitive neuromuscular blocking agents.
Anticholinesterase	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dose adjustment of antidiabetic agents may be necessary.
Antiemetics - Aprepitant - Phosaprepitant	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungals - Itraconazole - Ketoconazole	CYP3A4 INHIBITORS (and SUBSTRATES)
Antiviral - HIV Protease Inhibitors	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids can induce the metabolism of HIV protease inhibitors, resulting in decreased plasma concentrations.
Pharmacokinetic enhancer - Cobicistat	CYP3A4 INHIBITOR
Aromatase inhibitors - Aminoglutethimide	Aminoglutethimide-induced adrenal suppression may exacerbate the endocrine changes induced by long-term glucocorticoid therapy.
Calcium channel blocker - Diltiazem	CYP3A4 INHIBITORS (and SUBSTRATES)
Cardiac glycosides - Digoxin	Concomitant use of corticosteroids with cardiac glycosides may increase the risk of arrhythmias or digitalis toxicity associated with hypokalaemia. Serum electrolyte measurements, especially potassium levels, should be closely monitored in all patients taking these drugs concomitantly.
Oestrogens (including oral contraceptives containing oestrogens)	CYP3A4 INHIBITOR (and SUBSTRATE) Oestrogens may enhance the effects of hydrocortisone by increasing the concentration of transcortin and thereby decreasing the amount of hydrocortisone available to be metabolized. Dosage adjustment of hydrocortisone may be necessary if oestrogens are added to or deleted from a stable dosing regimen.
Grapefruit Juice	CYP3A4 INHIBITOR
Immunosuppressant - Cyclosporine	CYP3A4 INHIBITOR (and SUBSTRATE) Concomitant use may lead to increased activity of both cyclosporine and corticosteroids. Convulsions have been reported with concurrent use.
Immunosuppressant	CYP3A4 SUBSTRATES

Medicine class or type *- Medicine or substance*	*Interaction/Side Effect*
- Cyclophosphamide - Tacrolimus	
Macrolide antibiotics - Clarithromycin - Erythromycin	CYP3A4 INHIBITOR (and SUBSTRATE)
Macrolide antibiotics - Troleandomycin	CYP3A4 INHIBITOR
NSAIDs (non-steroidal anti-inflammatory drugs) - high dose acetylsalicylic acid	1) An increased incidence of bleeding and ulceration in the gastrointestinal tract is possible with concomitant administration of corticosteroids and NSAIDs. 2) Corticosteroids may increase the clearance of high doses of aspirin, which may lead to decreased salicylate plasma levels. Discontinuation of corticosteroid therapy may lead to increased salicylate plasma levels and an increased risk of salicylate toxicity.
Potassium lowering agents	When co-administering corticosteroids and potassium-lowering agents (such as diuretics), patients should be closely monitored for the development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids and amphotericin B, xanthines or beta-2 agonists. There have been reports that concomitant use of amphotericin B and hydrocortisone has been followed by cardiac enlargement and congestive heart failure.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is insufficient data on the use of hydrocortisone in pregnant women. Teratogenicity, in the form of cleft palate, has been observed in animal experiments. The mouse in particular appeared to be sensitive to this. However, the relevance for human pregnancy is limited. Hydrocortisone can be used when strictly indicated. Chronic use of higher doses should be avoided as much as possible given the risk of adrenocortical insufficiency in neonates.

Breast-feeding
Corticosteroids are excreted in breast milk; therefore, hydrocortisone should only be used during breastfeeding after careful consideration of the benefits and risks for the mother and child.

Fertility
There is no evidence that corticosteroids adversely affect fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

It should be taken into account the possible side effects of this medicine such as visual disturbances, muscle weakness, mood changes (euphoria and depression) and convulsions which may affect the ability to drive and use machines.

4.8 Undesirable effects

The following adverse reactions have been reported with the contraindicated intrathecal/epidural routes of administration: arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, convulsions, sensory disturbances. The frequency of these side effects is not known.

The following side effects have been seen with parenteral corticosteroid therapy. Its inclusion in this review does not mean that this specific side effect has been seen with the use of hydrocortisone. The frequency of the side effects below cannot be estimated from the available data and is listed in the table as not known.

Treatment with glucocorticoids, even at low doses, may cause the following side effects.

Table 2. Overview of side effects

System organ class	*Frequency not known (cannot be estimated from the available data)*
Infections and infestations	Opportunistic infection, masked infection, infection (activation of infection, including reactivation of tuberculosis)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Kaposi's sarcoma, pheochromocytoma crisis
Blood and lymphatic system disorders	Leucocytosis
Immune system disorders	Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Endocrine disorders	Cushing's syndrome, hypothalamic-pituitary-adrenal axis suppression, steroid withdrawal syndrome
Metabolism and nutrition disorders	Metabolic acidosis, sodium retention, fluid retention, hypokalaemic alkalosis, dyslipidaemia, glucose tolerance decreased; increased insulin requirement (or oral blood sugar lowering agents in diabetics), lipomatosis, stimulated appetite
Psychiatric disorders	Affective disorder (including depression, euphoric mood, affect lability, drug dependence, suicidal ideation), psychotic disorder (including mania, delusions, hallucinations and schizophrenia), mental disorders, personality change, confusional state, anxiety, mood swings, abnormal behaviour, insomnia, irritability, aggravation of pre-existing psychotic behaviour
Nervous system disorders	Epidural lipomatosis, increased intracranial pressure, benign intracranial hypertension, convulsions, amnesia, cognitive impairment, dizziness, headache
Eye disorders	Chorioretinopathy, cataract, glaucoma, exophthalmia, blurred vision (see also section 4.4)
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Congestive heart failure (in predisposed patients)
Vascular disorders	Thrombosis, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, gasping syndrome, hiccups
Gastrointestinal disorders	Peptic ulcer (with possible perforation and bleeding), intestinal perforation, gastric bleeding, pancreatitis, esophagitis, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea
Skin and subcutaneous tissue disorders	Angioedema, hirsutism, petechiae, ecchymosis, skin atrophy, erythema, hyperhidrosis, cutaneous striae, rash, pruritus, urticaria, acne
Musculoskeletal and connective tissue disorders	Muscle weakness, myalgia, myopathy, muscle atrophy, osteoporosis, osteonecrosis, pathological fracture, neuropathic arthropathy, arthralgia, growth retardation, spinal cord compression fracture, tendon rupture
Reproductive system and breast disorders	Irregular menstruation
General disorders and administration site conditions	Decreased healing, peripheral oedema, fatigue, malaise, injection site reaction
Investigations	Intraocular pressure 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 skin test responses, weight increased

Paediatric population

Infections, which are more serious or even fatal with concurrent use of glucocorticosteroids (e.g. chickenpox or measles), are more common in children than in adults.
Growth may be suppressed with long-term glucocorticoid treatment (see section 4.4).
Hypertrophic cardiomyopathy in premature infants (frequency not known)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no clinical syndrome of acute corticosteroid overdose.
Repeated frequent doses (daily or several times a week) over a long period of time may result in Cushing's syndrome.

In case of overdose, no specific antidote is available; treatment will be supportive and symptomatic.
Hydrocortisone is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, plain; Glucocorticoids, ATC code: H02AB09.

Glucocorticoids, natural and synthetic, are adrenal steroids.
Natural glucocorticoids (hydrocortisone and cortisone), which also have salt retention properties, are used as replacement therapy in conditions of adrenocortical deficiency.

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory effects as hydrocortisone. When administered parenterally in equimolar amounts, the two substances are equivalent in biological activity. The highly water-soluble sodium succinate ester of hydrocortisone allows direct intravenous administration of high doses of hydrocortisone in a small volume of solvent, and is particularly useful when high blood levels of hydrocortisone are required quickly. After intravenous injection of hydrocortisone sodium succinate, demonstrable effects become apparent within one hour and persist for a variable period of time.

The relative potency of methylprednisolone sodium succinate and hydrocortisone sodium succinate, as indicated by the reduction in eosinophil count, is 5:1 after intravenous administration. This is consistent with the relative oral potency of methylprednisolone and hydrocortisone.

Table 3. Relative potencies and equivalent doses of common corticosteroids

Corticosteroid	*Relative anti-inflammatory effect*	*Relative mineralocorticoid action*	*Equivalent dose (mg)*	*Plasma half-life (minutes)*
Cortisone	0.8	0.8	25	30
Hydrocortisone	1.0	1.0	20	90
Prednisone	4.0	0.8	5	60
Prednisolone	4.0	0.8	5	200
Triamcinolone	5.0	0.0	4.0	300
Methylprednisolone	5.0	0.0	4.0	180
Betamethasone	25.0	0.0	0.75	100-300
Dexamethasone	25-30	0.0	0.75	100-300
Fludrocortisone	10	125	-	200

Glucocorticoids diffuse through cell membranes and form complexes with specific cytoplasmic receptors. These complexes then penetrate to the cell nucleus, bind to DNA (chromatin) and stimulate the transcription of messenger RNA and the subsequent protein synthesis of various enzymes that are ultimately responsible for the effects observed after systemic use of glucocorticoids. Glucocorticoids affect the metabolism of most tissues, such as synthesis of specific liver enzymes, inhibition of glucose uptake and increased breakdown of proteins, ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). In addition, they modify the body's immune response to various stimuli.

The maximum pharmacological efficacy of glucocorticoids is achieved later than peak serum levels. This seems to indicate that most of the effects of these drugs are not due to a direct medicinal effect, but to a change in enzyme activity.

5.2 Pharmacokinetic properties

The pharmacokinetics of hydrocortisone in healthy male subjects showed non-linear kinetics when a single intravenous dose of hydrocortisone sodium succinate higher than 20 mg was administered, and the corresponding pharmacokinetic parameters of hydrocortisone are shown in Table 4.

Table 4. Mean (SD) pharmacokinetic parameters of hydrocortisone after single intravenous doses

	Healthy male adults (21-29 years; N = 6)			
Dose (mg)	5	10	20	40
Total exposure (AUC0-∞; ng.h/ml)	410 (80)	790 (100)	1480 (310)	2290 (260)
Clearance (CL; ml/min/m2)	209 (42)	218 (23)	239 (44)	294 (34)
Volume of distribution at steady state (Vdss; l)	20.7 (7.3)	20.8 (4.3)	26.0 (4.1)	37.5 (5.8)
Elimination half-life (t1/2; h)	1.3 (0.3)	1.3 (0.2)	1.7 (0.2)	1.9 (0.1)

AUC0-∞ = area under the curve from time zero to infinity.

Absorption
Following administration of single intravenous doses of 5, 10, 20 and 40 mg hydrocortisone sodium succinate in healthy male subjects, the mean peak values obtained 10 minutes after administration were 312, 573, 1095 and 1854 ng/ml, respectively. When administered intramuscularly, hydrocortisone sodium succinate is rapidly absorbed.

Distribution
Hydrocortisone is extensively distributed in the tissues, crosses the blood-brain barrier and is excreted in breast milk. The volume of distribution at steady state for hydrocortisone ranged from approximately 20 to 40 L (Table 4). 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 11β-HSD2 to cortisone, and further to dihydrocortisone and tetra-hydrocortisone. Other metabolites include dihydro-cortisol, 5α-dihydro-cortisol, tetra-hydrocortisol and 5α-tetra-hydrocortisol. Cortisone can be converted to cortisol by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).
Hydrocortisone is also metabolized by CYP3A4 to 6β-hydroxy-cortisol (6β-OHF), and 6β-OHF ranged from 2.8% to 31.7% of total metabolites produced, demonstrating high inter-individual variability.

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

Pharmacokinetics in special patient groups

Liver failure
No pharmacokinetic studies have been performed in patients with hepatic impairment. Literature data support that hydrocortisone has an enhanced effect in patients with liver disease as the metabolism and elimination of hydrocortisone is significantly reduced in these patients. A dose reduction should be considered.

5.3 Preclinical safety data

Mutagenesis/carcinogenicity
Hydrocortisone is negative in the bacterial mutagenicity test. Hydrocortisone induced chromosome aberrations in human lymphocytes in vitro and in mice in vivo. However, the biological relevance of these findings is not clear, as hydrocortisone did not increase tumour incidences in a 2-year carcinogenicity study.

Reproductive Toxicity
Corticosteroids have been shown to reduce fertility when administered to rats.
Corticosteroids have been shown to be teratogenic in several species when given at doses equivalent to human doses. In animal reproduction studies, glucocorticoids have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo foetal lethality, and intrauterine growth retardation. Cleft palate was observed in mice and hamsters with hydrocortisone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate E500(i)
Sodium dihydrogen phosphate monohydrate E339(i)
Disodium phosphate E339(ii)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

After reconstitution
After reconstitution with Water for Injections, the solution should be used immediately.

After dilution for intravenous infusion
Chemical and physical in-use stability has been demonstrated as follows:

- At a concentration of 0.1 mg/mL hydrocortisone, the diluted solution is stable for 6 hours at 2–8°C and at 25°C when diluted with:
    - sodium chloride 9 mg/ ml (0.9%) solution
    - 5% glucose solution
    - sodium chloride 9 mg/ ml (0.9%) and 5% glucose solution
- At a concentration of 1 mg/mL hydrocortisone:
    - Stable for 3 hours at 25°C when diluted with sodium chloride 9 mg/ ml (0.9%) or 5% glucose
    - Stable for 6 hours at 2–8°C when diluted with sodium chloride 9 mg/ ml (0.9%) or 5% glucose
    - Stable for 6 hours at 2–8°C and 25°C when diluted with sodium chloride 9 mg/ ml (0.9%) and 5% glucose solution

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not exceed 24 hours at 2–8°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 storage conditions. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

7 ml glass vials type III, sealed with a 20mm Sterile rubber stopper and aluminium flip off caps suitable for parenteral preparation.
Boxes of 1 and 10 vials are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Instructions for reconstitution
Under aseptic conditions, add 2 ml of water for injection to the vial containing sterile powder.

Intravenous or intramuscular injection
Prepare the solution as described above. No further dilution is required for intravenous or intramuscular injection.

Intravenous infusion
First prepare the solution as described above. The 100 mg solution may then be added to 100 to 1000 ml of one of the following solutions:
- aqueous 5% glucose solution
- sodium chloride 9 mg/ ml (0.9%) solution
- sodium chloride 9 mg/ ml (0.9%) with 5% glucose solution

Stability after dilution
- 0.1 mg/mL: chemically and physically stable for 6 hours at 2–8°C or 25°C in all tested diluents.
- 1 mg/mL:
    - Stable for 3 hours at 25°C in sodium chloride 9 mg/ ml (0.9%) or 5% glucose
    - Stable for 6 hours at 2–8°C in sodium chloride 9 mg/ ml (0.9%) or 5% glucose
    - Stable for 6 hours at 2–8°C and 25°C in sodium chloride 9 mg/ ml (0.9%) with 5% glucose

From a microbiological point of view, the product should be used immediately.

The pH of the reconstituted solution prepared as described above is between 7 and 8.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Medochemie Limited
1-10 Konstantinoupoleos Street
3011 Limassol Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

Hydrocortison Medochemie 100 mg poeder voor oplossing voor injectie/infusie RVG **134247**

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 18 mei 2026

10. DATE OF REVISION OF THE TEXT