1. NAME OF THE MEDICINAL PRODUCT
Hydrocortison Orion 10mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10mg hydrocortisone.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hydrocortison Orion 10mg Tablet is a white, round, flat bevelled-edged, scored uncoated tablet approx. 7 mm diameter with code ORN 45.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Adrenocortical insufficiency (Addison's disease), diminution of anterior pituitary function (hypopituitarism), congenital adrenal hyperplasia. Conditions where systemic glucocorticoid therapy is indicated.

4.2 Posology and method of administration
Posology
As replacement therapy, 20 to 30mg daily, usually approximately 2/3 of this amount in the morning and 1/3 in the early evening. If necessary, the morning dose may be taken in 2 parts. In the other indications, 40 to 200mg daily; in short-term use in special indications, even higher doses.
Paediatric population
In children, the dosage is individual. In adrenocortical insufficiency, 7.5 to 15mg/m²/day divided in 3 equal doses (first thing in the morning, in the afternoon, and late in the evening); the morning dose may also be larger than the other doses. In congenital adrenal hyperplasia, usually 10mg/m²/day divided in 3 doses. In hypopituitarism, 2.5mg 3 times daily.
Dosing in special situations
Hydrocortisone replacement therapy:
In patients receiving hydrocortisone replacement therapy, the dosage of Hydrocortison should be increased 2–4-fold in stressful situations, such as in connection with injuries, infections or surgery. If necessary, the patient should be switched to parenteral treatment.
Pharmacological glucocorticoid therapy:
Long-term systemic glucocorticoid therapy causes adrenocortical insufficiency that may persist for months after treatment cessation. Therefore, the dosage of Hydrocortison should be increased in stressful situations such as in connection with infections.
In order to avoid glucocorticoid withdrawal syndrome, long-term treatment with corticosteroids should be discontinued gradually over several weeks. Dosing on alternate days reduces the risk of adrenocortical insufficiency and of the withdrawal syndrome associated with treatment cessation.

4.3 Contraindications
Tuberculosis and other systemic acute and chronic bacterial, fungal, viral and parasitic infections without appropriate medication
Vaccines containing live, attenuated viruses or bacteria should not be given to a patient receiving high-dose corticosteroid therapy during treatment-induced immunodeficiency.
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
In pharmacological doses, hydrocortisone treatment may increase the prevalence of complications of many acute and latent diseases and lead to the worsening (or onset) of some diseases. Therefore, caution should be observed in patients diagnosed with diabetes, gastric or duodenal ulcer, osteoporosis or glaucoma. Caution should also be observed in patients with cardiac insufficiency, recent myocardial infarction, hypertension, renal impairment, hepatic impairment, history of corticosteroid-induced myopathy, epilepsy, hypothyroidism, inflammatory bowel disease and diverticulitis, or in patients who have recently undergone an anastomosis operation. In patients receiving high doses of corticosteroids, there may be little or no signs of peritoneal irritation caused by gastrointestinal perforation.
Particular caution is required when considering systemic pharmacological corticosteroid therapy in patients with a current or previous severe mood disorder, including depression or bipolar disorder, psychosis, or a history of steroid-induced psychosis. The patients or their caregivers should be encouraged to talk to a physician if any worrisome psychiatric symptoms occur, especially when depression or thoughts of self-harm are suspected. The patients or their caregivers should be informed that psychiatric disorders may occur both upon dose reduction or discontinuation of the use of a systemic steroid, and immediately after these. However, these reactions have been reported rarely.
Corticosteroid clearance from the body may be reduced in patients with hypothyroidism, and increased in patients with hyperthyroidism.
The lowest possible corticosteroid dosage should be used, and when the dosage can be reduced, it should be done gradually. Discontinuing long-term corticosteroid therapy may cause withdrawal symptoms (see section 4.8).
Discontinuing corticosteroid therapy too rapidly may result in drug-induced secondary adrenocortical insufficiency, which can be minimised by reducing the dose gradually. This kind of relative insufficiency may persist for months after treatment withdrawal. If any kind of stressful situations occur during this time, corticosteroid therapy should be reinstituted. If the patient is already taking steroids, an increase in the dosage may be required. As mineralocorticoid secretion may be reduced, the patient should be given concomitant salt and/or mineralocorticoids.
Corticosteroids increase the susceptibility to infections and may mask the symptoms of an infection. As varicella or measles may be particularly dangerous during immunodeficiency induced by corticosteroid therapy, particular caution is required regarding varicella, measles or *herpes zoster* infections. Patients receiving immunocompromising doses of corticosteroids who have not been vaccinated or are unsure of whether they have had varicella/measles should be instructed to avoid exposure to varicella/measles. If exposure occurs, the patient should seek urgent medical care.
Caution should be observed in patients who have had tuberculosis, as latent disease may be reactivated.
Corticosteroids may activate latent amoebiasis or strongyloidiasis, or aggravate an active-phase disease. Therefore, latent or active amoebiasis and strongyloidiasis should preferably be ruled out before instituting corticosteroid therapy in patients at risk or with symptoms indicating either of these.
Vaccines containing live, attenuated viruses or bacteria should not be administered to patients receiving high-dose corticosteroid therapy during immunodeficiency induced by the treatment. The administration of these vaccines should generally be avoided during corticosteroid therapy. When using other types of vaccines, their protective effect may be weaker than usual due to immunodeficiency.
Phaeochromocytoma crisis
Phaeochromocytoma-related crises, which may be fatal, have been reported after administration of systemic corticosteroids. Patients with suspected or diagnosed phaeochromocytoma should only be given corticosteroids after a careful risk-benefit assessment
Visual disturbance
Visual disturbances may be reported in connection with systemic or topical corticosteroid use. Patients who experience symptoms such as blurred vision or other visual disturbances should be referred to an ophthalmologist for an assessment of possible causes of the symptoms. These may include cataract, glaucoma or rare conditions such as central serous chorioretinopathy, which have been reported after systemic or topical corticosteroid use.
Long-term corticosteroid use may cause cataract and glaucoma, which may damage the optic nerve, and promote the onset of secondary fungal and viral ocular infections. Corticosteroids should be used with caution in patients with an ocular *herpes simplex* infection, as the infection may be aggravated and the cornea may rupture.
Glucocorticoid therapy may affect blood coagulation. Caution should be observed in the concomitant use of medicines influencing blood coagulation (such as warfarin or ASA products).
Paediatric and elderly patients
The adverse effects of systemic glucocorticoid therapy may be more pronounced in elderly persons and in children.
In infants, children and adolescents, glucocorticoid therapy may cause growth retardation, which should be taken into consideration. The lowest effective dosage should be used in the treatment to minimise hypothalamic-pituitary-adrenal axis suppression and growth retardation. The growth and development of infants and children receiving long-term corticosteroid therapy should be monitored closely.
Hypertrophic cardiomyopathy was reported after administration of hydrocortisone in premature infants, and therefore appropriate diagnostic examinations and monitoring of cardiac function and structure should be performed in these patients.
Excipients
Hydrocortison tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacokinetic interactions
Phenytoin, phenobarbital, rifabutin, barbiturates, carbamazepine, primidone, rifampicin, thyrostatics and St. John's wort, as well as the antiretroviral medicinal agents efavirenz and nevirapine, increase hydrocortisone clearance and reduce its half-life. This may require adjusting the hydrocortisone dose.
Ketoconazole, itraconazole, posaconazole, voriconazole, erythromycin, telithromycin, clarithromycin, ritonavir and grapefruit juice may inhibit hydrocortisone metabolism and thus increase its blood concentrations. Adjustment of the hydrocortisone dosage should be considered in patients receiving long-term prophylaxis with any antibiotic.
Concomitant use with CYP3A inhibitors such as products containing cobicistat is expected to increase the risk of systemic adverse effects. The use of this combination must be avoided unless the benefit exceeds the increased risk of systemic corticosteroid adverse effects, in which case patients should be monitored for systemic corticosteroid adverse effects.
Oestrogen products and oral contraceptives may increase the plasma concentrations of hydrocortisone.
Glucocorticoids increase salicylate clearance. Caution should be observed if the glucocorticoid dose is reduced after long-term concomitant use.
Pharmacodynamic interactions
Hydrocortisone may elevate blood pressure. This should be taken into account in patients receiving concomitant antihypertensive medication.
Hydrocortisone may reduce or, in some cases, increase the effect of anticoagulants. Caution should be observed in the concomitant use of warfarin and systemic glucocorticoids.
The effect of antidiabetics (including insulin) may be reduced in concomitant use with corticosteroids, and increasing the dose of the antidiabetic may be necessary.
When used with anticholinesterases, corticosteroids may cause muscle weakness in patients with *myasthenia gravis*.
Systemic glucocorticoid therapy increases the risk of hypokalaemia in patients receiving diuretics, amphotericin B, cardiac glycosides, theophylline or $beta_2$ sympathomimetics. Patients requiring concomitant treatment with these medicinal agents should be monitored for signs and symptoms of hypokalaemia. If hypokalaemia occurs, it increases the toxicity of cardiac glycosides such as digoxin.
Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid with glucocorticoids increases the risk of ulceration and gastrointestinal bleeding.
Glucocorticoids increase the clearance of salicylates. Caution should be observed if the glucocorticoid dose is reduced after long-term concomitant use.
Corticosteroids may inhibit the growth-promoting effect of somatropin.
Mifepristone therapy may reduce the effect of corticosteroids for 3 to 4 days.
The concomitant use of fluoroquinolones and glucocorticoids may increase the risk of tendon rupture.
Glucocorticoids may decrease the efficacy of vaccinations and increase the risk of neurological complications related to vaccinations. Live virus vaccines may cause an infection in patients receiving hydrocortisone. Vaccines containing live, attenuated viruses or bacteria should not be administered to patients receiving high-dose corticosteroid therapy during immunodeficiency induced by the treatment.

4.6 Fertility, pregnancy and lactation
Pregnancy
Hydrocortisone crosses the placenta. Systemic corticosteroid therapy during pregnancy, other than replacement therapy, should be approached with caution. However, treatment should not be avoided if clearly indicated. If the mother has received hydrocortisone in pharmacological doses during pregnancy, the neonate should be monitored to detect potential adrenal insufficiency.
Corticosteroid therapy during pregnancy has been associated with foetal growth reduction, particularly in long-term use, and with insignificant contraction of the ductus arteriosus in isolated cases. During late pregnancy, hydrocortisone may cause adverse effects to the foetus that are similar to those of long-term therapy in general.
In animal tests, corticosteroids have caused cheiloschisis and palatoschisis. No increase in palatoschisis rates has been demonstrated in humans.
Breast-feeding
Hydrocortisone is excreted in human milk. Breast-feeding is possible during low-dose pharmacological treatment. If the doses are > 100mg/day, breast-feeding should be avoided for a few hours after taking the medicine. If the mother uses large doses of systemic corticosteroids for a long time, the breast-feeding child's adrenal function may be suppressed to some extent.
Fertility
Corticosteroids may decrease the quality of spermatozoa and cause amenorrhoea.

4.7 Effects on ability to drive and use machines
Hydrocortisone does not usually impair the ability to drive a car or use machines. In high-dose long-term therapy, some patients may have mood fluctuations and mental instability, which may impair performance in traffic. Hydrocortisone may also cause muscle weakness, muscle

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wasting, vertigo, visual field defects, mood swings and mental instability in some patients. If these occur, the patient must not drive a car or use machinery.

4.8 Undesirable effects

The adverse effects of hydrocortisone are similar to those of other glucocorticoids. It also has a mineralocorticoid effect. Treatment duration and the dose used influence the occurrence of adverse effects. In high-dose long-term therapy, adverse effects regularly develop.
In high-dose long-term therapy, hydrocortisone causes adrenocortical insufficiency; therefore, stress such as surgery or infections may lead to hypotension, hypoglycaemia and even death, unless the steroid dose is increased to accommodate for the stress.
Abrupt discontinuation of long-term steroid treatment results in glucocorticoid withdrawal syndrome. Symptoms may include fever, muscle and joint pain, asthenia, nausea, increased intracranial pressure and hypotension (see section 4.4).
Glucocorticoids may cause allergy and anaphylactic reactions.
Frequency categories for adverse effects are defined as follows:
Common (>1/100), Uncommon (≥1/1,000 to <1/100), Rare (<1/1,000), Not known (cannot be estimated from the available data).

	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				Leukocytosis
Immune system disorders	Increased susceptibility to infections, masked infection symptoms	Allergic reactions		Angioedema, aggravation of pre-existing infection, activation of latent infection
Endocrine disorders	Suppression of endogenous ACTH and cortisol secretion (in long-term use), symptoms of Cushing's syndrome, worsening/onset of diabetes			Secondary lack of adrenocortical and pituitary response (particularly in stressful situations, e.g. because of trauma, surgery or disease), reduced sugar tolerance
Metabolism and nutrition disorders	Hypokalaemia, sodium retention	Increased appetite		Hypokalaemic alkalosis, increased calcium excretion, fluid accumulation, negative nitrogen balance due to protein catabolism
Psychiatric disorders		Mood fluctuations, depression, mania, psychoses, insomnia		Mood disorders, behavioural disturbances, irritability, anxiety, sleep disturbances, cognitive dysfunction, including confusion and amnesia
Nervous system disorders			Increased intracranial pressure (pseudotumor cerebri), convulsions	Vertigo, headache
Eye disorders		Increased intraocular pressure, glaucoma, cataract		Papilloedema, thinning of the cornea or the sclera, exophthalmos, blurred vision (see also section 4.4)
Cardiac disorders	Exacerbation of cardiac insufficiency			Myocardial rupture caused by recent myocardial infarction, hypertrophic cardiomyopathy in premature infants
Vascular disorders	Hypertension	Thromboses		
Respiratory, thoracic and mediastinal disorders				Hiccups
Gastrointestinal disorders			Pancreatitis	Gastrointestinal ulceration that may be associated with perforation and haemorrhage (see 4.4 and 4.5); ulcerative oesophagitis; perforation of the small and large intestine; abdominal distension; dyspepsia; candidiasis of the oesophagus
Skin and subcutaneous tissue disorders	Skin atrophy (thinning and degeneration), slow healing and scarring of tissue damage, acne, striae, bruising tendency, ecchymosis			Petechiae, erythema, telangiectasia, increased sweating, allergic dermatitis, urticaria, hirsutism
Musculoskeletal and connective tissue disorders	Muscular atrophy, muscle weakness, osteoporosis		Aseptic bone necrosis, tendon rupture	Steroid-induced myopathy, spinal compression fracture, pathological long bone fracture
Reproductive system and breast disorders				Menstrual disorders, amenorrhoea
General disorders and administration site conditions	Growth retardation in children, oedema			Nausea, malaise
Investigations				Weight gain

Corticosteroid therapy may also cause increased coagulation tendency, hyperlipidaemia and nephroliths. Corticosteroid therapy may also reduce semen quality (see section 4.6).

Paediatric population and the elderly

The adverse effects of systemic corticosteroid therapy may be more pronounced in elderly patients and children.

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. You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by calling Tel: 03-78835550, or visiting the website npra.moh.gov.my (Public→ Reporting Side Effects to Medicines (ConSERF) or Vaccines).

4.9 Overdose

Acute, massive hydrocortisone overdose is unlikely. Considerably high single doses are tolerated without serious adverse effects. The treatment for oral overdose is supportive; if necessary, activated charcoal may be administered and gastric lavage performed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group, ATC code: Corticosteroids for systemic use, Glucocorticoids, H02AB09.
Hydrocortisone, i.e. cortisol, is a natural hormone of the adrenal cortex. Like other glucocorticoids, it exerts its effects by binding to steroid receptors in the cytoplasm. This results in the formation of a steroid-receptor complex that passes into the nucleus, where it binds to the DNA and thus regulates the transcription of many genes and also protein synthesis. Its effects are mediated by e.g. increased lipocortin synthesis.
The effect of glucocorticoids is catabolic, especially in muscle tissue. They decrease the production of lymphokines and eicosanoids and the amount of lymphatic tissue, and they weaken the immune response and exert an anti-inflammatory effect regardless of the cause of the inflammation. They also reduce fibroblast activity and scarring. Glucocorticoids reduce ACTH secretion and suppress the pituitary-adrenal axis. Hydrocortisone exerts some mineralocorticoid effect. After a 250mg single dose of hydrocortisone, ACTH secretion is suppressed for approximately 1 to 1.5 days.

5.2 Pharmacokinetic properties

Hydrocortisone is rapidly and completely absorbed from the gastrointestinal tract. Due to first-pass metabolism, its availability varies between 25% and 90%. The peak plasma concentration of hydrocortisone is reached 1 to 2 hours after dosing. It binds to transcortin and albumin in plasma. In low concentrations, 10% of the hydrocortisone is in free form, while in higher concentrations, transcortin binding capacity is saturated, and the proportion of free medicine may increase to 40% to 50%. The volume of distribution is 0.4 to 0.7 l/kg. The mean pharmacological half-life of hydrocortisone is 1.5 h, but the half-life of its biological effect is considerably longer, approximately 10 hours. Hydrocortisone crosses the placenta and is excreted in breast milk in low quantities. Hydrocortisone elimination may be slower in hepatic diseases and shorter in thyrotoxicosis.

5.3 Preclinical safety data

In animal tests, corticosteroids have caused cheiloschisis and palatoschisis.

6.1 List of excipients

Lactose monohydrate
Maize starch
Talc
Gelatin
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C. Store in the original package. Protect from light.
Keep out of the reach of children.
See the package for the expiry date.
Do not use the medicine after the stated date.

6.5 Nature and contents of container

Brown glass jar (type III); 100 tablets.

6.6 Special precautions for disposal

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

7. Manufacturered by

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8. Product Owner:

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9. Product Registration Holder

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MAL15085015AZ

11. Date of last revision

26 November 2021

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