

## **VI.2 Elements for a Public Summary**

Hydrocortisone (i.e. cortisol) is a natural hormone that belongs to a class of medicines called corticosteroids. Corticosteroids mimic the effects of hormones body produces naturally in adrenal glands that are located on top of each kidney. These hormones are essential for life. When prescribed in doses that exceed body's usual levels, corticosteroids suppress inflammation. This can reduce the signs and symptoms of inflammatory conditions. Corticosteroids also suppress immune system, which can e.g. help control conditions in which immune system mistakenly attacks its own tissues.

Hydrocortison Orion tablets are used in:

- children and adolescents to replace hydrocortisone because part of the adrenal gland is not working properly (congenital adrenal hyperplasia, adrenal insufficiency)
- emergency treatment of severe asthma, drug hypersensitivity reactions, serum sickness (hypersensitivity reaction to proteins), localized swelling of the skin and/or mucous membranes (angioedema), and life-threatening allergic reactions (anaphylaxis)

### **VI.2.1 Overview of disease epidemiology**

#### Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is an inherited disorder of the adrenal glands. The condition is often diagnosed at birth. People with congenital adrenal hyperplasia lack an enzyme that adrenal gland needs to make the hormones (cortisol, aldosterone). The most common enzymatic defect is cytochrome P450 21-hydroxylase (CYP21) deficiency accounting for approximately 95% of cases. The person with CAH will either not produce adrenal hormones or will produce them in the wrong amounts (e.g. too little cortisol, too much androgens). There is no cure, but CAH can be managed with hormonal treatment e.g. hydrocortisone. Congenital adrenal hyperplasia can affect both boys and girls. About 1 in 10,000 to 18,000 children are born with congenital adrenal hyperplasia.

#### Adrenal insufficiency

Adrenal insufficiency is a hormonal-disorder that occurs when the adrenal glands do not produce enough of certain hormones. Adrenal insufficiency can be primary or secondary.

Primary adrenal insufficiency, also called Addison's disease, occurs when the adrenal glands are damaged and cannot produce enough of the hormone cortisol and often the hormone aldosterone. Addison's disease affects one to four of every 100,000 people, in all age groups and both sexes. Addison's disease can be life-threatening.

Secondary adrenal insufficiency occurs when the pituitary gland-a bean-sized organ in the brain-fails to produce enough adrenocorticotropin (ACTH), a hormone that stimulates the adrenal glands to produce cortisol. If ACTH output is too low, cortisol production drops. Eventually, the adrenal glands can shrink due to lack of ACTH stimulation. Secondary adrenal insufficiency is much more common than Addison's disease.

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## Allergic/hypersensitivity reactions, asthma

Allergies occur when immune system reacts to a foreign substance such as pollen, bee venom or pet dander. Those are called allergens. In allergy immune system makes antibodies that identify a particular allergen as something harmful. When an allergic person comes into contact with the certain allergen, the immune system's reaction can inflame skin, sinuses, airways or digestive system. The severity of allergies varies from person to person and can range from minor irritation to anaphylaxis — a potentially life-threatening emergency.

Angioneurotic edema (angioedema) is caused by triggers that stimulate mast cells to release histamine and other chemicals into bloodstream causing swelling that affects deeper layers in skin, often around eyes and lips. Allergic reactions are common trigger of acute angioedema. However, sometimes it's not possible to pinpoint the cause of angioedema, especially when condition becomes chronic or recur. Serious angioedema can be life-threatening if swelling causes throat or tongue to block the airway. Hereditary angioedema is a rare inherited (genetic) condition that can cause sudden, severe and rapid swelling of face, arms, legs, hands, feet, genitalia, digestive tract and airway.

Serum sickness describes a delayed immune system response e.g. to certain kinds of medications. Serum sickness is similar to an allergy, in that the body mistakenly identifies a protein from the antiserum or medication as harmful and activates the immune system to fight against it. The most common cause of serum sickness is the antibiotic agent penicillin. Serum sickness will usually develop within 7 - 10 days after initial exposure, but sometimes it can take as long as 3 weeks. Symptoms include fever, general ill feeling, hives, itching, joint pain, rash and swollen lymph nodes.

Asthma is a condition in which airways narrow and swell and produce extra mucus. This can make breathing difficult and trigger coughing, wheezing and shortness of breath. Development of asthma is probably due to a combination of environmental and genetic (inherited) factors. Exposure to various substances that trigger allergies (allergens) and irritants can trigger signs and symptoms of asthma.

### **VI.2.2 Summary of treatment benefits**

Hydrocortisone is well established drug for the treatment of acute and chronic CAH. The efficacy of hydrocortisone has been demonstrated by clinical practice rather than clinical studies meeting today's standards for a randomised controlled trial. Before the introduction of glucocorticoids most patients with the most severe type of CAH died within the neonatal period or the first months of life.

The role of hydrocortisone in treatment of especially chronic adrenal insufficiency has been firmly established by long-term clinical experience. Treatment of adrenal insufficiency involves substituting the hormones that the adrenal glands are not producing. Cortisol is replaced with a synthetic glucocorticoid such as hydrocortisone

Corticosteroids, such as hydrocortisone, are also frequently used drugs that mediate immunosuppressive and anti-inflammatory effects. They relieve the inflammation, pain and discomfort

of many different diseases and conditions. They lessen swelling, redness, itching, and allergic reactions. Therefore they are often used as part of the treatment for a number of different diseases, such as severe allergies or asthma. High doses of corticosteroids are usually required in patients with severe diseases involving major organs. In intensive or emergency therapy, parenteral (given e.g. intravenously or injected in muscle) administration may be required.

**VI.2.3 Unknowns relating to treatment benefits**

Not applicable.

**VI.2.4 Summary of safety concerns**

**Important identified risks**

Risk	What is known	Preventability
<p>Increased likelihood to get infections and masking of symptoms of infection</p>	<p>People who receive corticosteroids, such as hydrocortisone, for a long period of time are prone to infections as their immune system can become weak. This is the case especially if high doses are administered.</p> <p>Infections may become more severe than they usually would be and the symptoms that would usually be used to identify such infections can be hidden.</p>	<p>Any current infections and medical history of infections should be taken into account before therapy is initiated.</p> <p>Hydrocortisone should not be given to patients who have microbial infection in their body system without appropriate antimicrobial drug therapy.</p> <p>Live vaccines should not be given during high-dose hydrocortisone therapy.</p> <p>Special attention should be paid for signs and symptoms of infection during hydrocortisone therapy and doctor should be contacted if symptoms appear.</p> <p>Close contact with people who have acute infections should be avoided.</p> <p>Special caution is necessary in unvaccinated patients and in patients without a definite history of chickenpox/measles who receive immunosuppressive doses of corticosteroids. If they are exposed to chickenpox/measles they should seek urgent medical attention.</p>

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
Symptoms of too little or too much cortisol in body	<p>Long-term use of corticosteroids may cause suppression of body's own corticosteroid production.</p> <p>Too much corticosteroids in body, especially for long-time, can cause symptoms of Cushing syndrome — a fatty hump between shoulders, a rounded face, and pink or purple stretch marks on skin. Cushing syndrome can also result in high blood pressure, bone loss and, on occasion, diabetes.</p> <p>The severity and duration of these conditions (too little or too much cortisol in body) vary by the patient and depend on the dose, dosing interval, time of day of administration, and length of therapy.</p> <p>If the dose of hydrocortisone is reduced too rapidly serious problems may occur.</p>	<p>Dose should be adjusted individually using the smallest effective dose.</p> <p>Long-term corticosteroid therapy should not be stopped abruptly. The dose should be decreased gradually. If the patient's own corticosteroid production is suppressed, she/he should receive additional corticosteroids in case of stressful situations, such as illness or injury.</p>
Eye disorders	<p>The occurrence of secondary fungal and viral eye infections may increase in patients receiving corticosteroids and there is a risk of corneal perforation, in patients with ocular herpes simplex infection.</p> <p>Long term corticosteroid use may cause cataract, bulging of the eyes, or increased eye pressure, which may lead to glaucoma and a potential subsequent injury to the optic nerve.</p> <p>Blurred vision or other visual disturbances may appear during treatment. Those can be symptoms cataract, glaucoma or rare diseases such as central</p>	<p>Special caution should be administered when treating patients with ocular infections.</p> <p>Medical history of increased eye pressure, cataract or glaucoma should be taken into account and discussed with doctor.</p> <p>Doctor needs to be contacted, if patient experiences blurred vision or other visual disturbances.</p>

Risk	What is known	Preventability
	serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.	
Bones become weak and brittle (osteoporosis)	Osteoporosis is a common, yet rarely recognized, adverse effect of prolonged high-dose corticosteroid treatment.	<p>Medical history of osteoporosis should be taken into account and discussed with doctor.</p> <p>Vitamin D and calcium supplements, healthy diet, weight-bearing exercise and certain medications may help to prevent bone loss or strengthen already weak bones.</p>
Development or worsening of diabetes	Corticosteroids, including hydrocortisone, may increase blood glucose concentration, exacerbate diabetes and predispose patients receiving long-term corticosteroid treatment to diabetes.	<p>Medical history of diabetes, glucose intolerance or increased blood sugar should be taken into account and discussed with doctor.</p> <p>The dose of insulin or other antidiabetic drugs may need to be adjusted.</p>
Psychiatric adverse reactions (depression, mania, psychosis)	<p>Psychiatric disorders, such as euphoria, insomnia, mood alterations, personality changes, deep depression, or definite psychotic symptoms, may occur in connection with the use of corticosteroids. During the corticosteroid medication, the condition may become exacerbated in emotionally unstable patients or those with a psychotic tendency.</p> <p>Potentially serious psychiatric adverse effects may occur during therapy. Typically, symptoms appear after a couple of days or weeks from starting the treatment.</p> <p>Psychiatric effects have been reported on cessation of the use of corticosteroids. The frequency of such effects is unknown.</p>	<p>Medical history of mental problems should be taken into account and discussed with doctor.</p> <p>Most psychiatric reactions recover after either dose reduction or treatment withdrawal, although specific treatment may be needed.</p> <p>Patients and/or their carers should contact doctor, if psychiatric symptoms develop, especially if depressed mood or suicidal thoughts are suspected.</p> <p>Patients and/or their carers should be aware of the potential psychiatric effects which may occur at reduction of the corticosteroid dose or immediately after cessation of their use.</p>

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
Withdrawal syndrome	<p>Withdrawal syndrome can occur if long-term hydrocortisone therapy is stopped abruptly.</p> <p>Withdrawal syndrome may include symptoms such as: fever; headaches; nausea; vomiting; lethargy; loss of appetite; weight loss; eye or eyesight problems; rhinitis; muscle pain or tenderness; joint pain; skin problems such as painful, itchy skin or peeling of the skin.</p>	Dose should be reduced gradually after long-term therapy.
Interactions with anti-inflammatory pain medicines	Concomitant use of corticosteroids with anti-inflammatory pain medicines may increase the risk of bleedings and ulcers in stomach and bowel.	Anti-inflammatory pain medicines should be administered with special caution.
Peptic ulcers and bleeding from stomach or intestine	<p>Peptic ulcers are sores that develop on the inside lining of esophagus, stomach and the upper portion of small intestine. The most common symptom of a peptic ulcer is abdominal pain.</p> <p>Bleeding can occur as slow blood loss that leads to anemia or as severe blood loss that may require acute hospitalization.</p> <p>There is no consensus on whether peptic ulcers developing during the treatment are caused by corticosteroids. However corticosteroid therapy may mask the symptoms of peptic ulcers, allowing perforation or bleeding to develop without any notable pain.</p>	<p>Medical history of diseases/conditions affecting alimentary canal and concomitant medications should be taken into account and discussed with doctor.</p> <p>Doctor should be contacted immediately in case of symptoms of stomach pain and bleeding from the anus, black or bloodstained stools and/or vomiting blood.</p>

## Important potential risks

<b>Risk</b>	<b>What is known (Including reason why it is considered a potential risk)</b>
Administration in elderly patients	Treatment of elderly patients, particularly if long term, should be planned bearing in mind the more serious consequences of the common side effects of corticosteroids in old age, especially osteoporosis, diabetes, hypertension, susceptibility to infection and thinning of the skin.
Administration in children	Pharmacological corticosteroid therapy may cause growth retardation in infancy, childhood and adolescence. Treatment should be limited to the minimum effective dosage in order to minimise suppression of the hypothalamo-pituitary-adrenal axis and growth retardation. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored.
Administration during pregnancy and lactation	<p>Hydrocortisone crosses the placenta. Besides replacement therapy, other systemic corticosteroid therapy during pregnancy should be regarded 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 for adrenal insufficiency.</p> <p>Corticosteroid therapy during pregnancy has been associated with foetal growth reduction, particularly in long-term use, and with insignificant contraction of the ductus arteriosus (a blood vessel that connects two major arteries in fetus' heart).</p> <p>During late pregnancy, hydrocortisone may cause adverse effects to the foetus that are similar to those of long-term therapy in general.</p>
Interaction with anticoagulants (medication used to prevent blood clots)	The effect of hydrocortisone on anticoagulants varies. Both increased and decreased effects on blood clotting have been reported in concomitant administration. Regular and frequent check-ups and lab tests may be necessary during concomitant therapy. Dosage of anticoagulant medicine may need to be adjusted.

### **VI.2.5 Summary of risk minimisation measures by safety concern**

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Hydrocortisone Orion can be found in the national authority's web page

This medicine has no additional risk minimisation measures.

**VI.2.6 Summary of changes to the Risk Management Plan over time**

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.2	11.9.2014	<p><b>Important identified risks</b></p> <ul style="list-style-type: none"> <li>- Increased susceptibility to infections and masking of symptoms of infection</li> <li>- Symptoms of hypo- or hypercortisolism</li> <li>- Eye disorders</li> <li>- Osteoporosis</li> <li>- Development or aggravation of diabetes</li> <li>- Psychiatric adverse reactions (depression, mania, psychosis)</li> <li>- Withdrawal syndrome</li> <li>- Interactions with NSAIDs</li> <li>- Peptic ulcers and gastrointestinal hemorrhage</li> </ul> <p><b>Important potential risks</b></p> <ul style="list-style-type: none"> <li>- Administration in elderly patients</li> <li>- Administration in children</li> <li>- Administration during pregnancy and lactation</li> </ul> <p><b>Missing information</b> None</p>	First approved version of the RMP



<b>Version</b>	<b>Date</b>	<b>Safety Concerns</b>	<b>Comment</b>
2	28.4.2017	Same as in version 1.2	Information regarding eye disorders has been added based on updated product information.