SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20mg hydrocortisone

Excipients with known effect:

Each tablet contains 146.75 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White to off white, elliptical shape, flat, bevelled edge tablet with “BL 20” on one side and a breakline on other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Corticosteroid

- For use as replacement therapy in congenital adrenal hyperplasia in children.
- Treatment of adrenal insufficiency in children and adolescents < 18 years of age.
- Emergency treatment of severe bronchial asthma, drug hypersensitivity reactions, serum sickness, angioneurotic oedema and anaphylaxis in adults and children.
- Pre-operatively, and during serious trauma or illness in children with known adrenal insufficiency or doubtful adrenocortical reserve.

Hydrocortisone tablets are indicated in adults and children aged from 1 month to 18 years where the dose of 10 mg, 20mg and tablet formulation is considered appropriate

4.2 Posology and method of administration

Posology

Dosage must be individualised according to the response of the individual patient. The lowest possible dosage should be used.

In patients requiring replacement therapy, the daily dose should be given when practicable, in two doses. The first dose in the morning should be larger than the second dose in the evening, thus simulating the normal diurnal rhythm of cortisol secretion.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g. surgery, infection, trauma). During stress it may be necessary to increase the dosage temporarily

To avoid hypoadrenalism and/or a relapse of the underlying disease, it may be necessary to withdraw the drug gradually (see section 4.4).

Replacement therapy

Paediatric population

In congenital adrenal hyperplasia, 9–15 mg/m^2/day divided in 3 doses, adjusted according to response.

In adrenocortical insufficiency, 8–10 mg/ m^2/day divided in 3 doses, adjusted according to response. Higher doses may be needed.

In chronic adrenocortical insufficiency, the dosage should be approximately 0.4 to 0.8mg/kg/day in two or three divided doses, adjusted to the needs of the individual child.

Pre-operative use:

Anaesthetists must be informed if the patient is taking corticosteroids or has previously taken corticosteroids.

When long term treatment is to be discontinued, the dose should be gradually reduced over a period of weeks or months, depending on dosage and duration of therapy (see section 4.4, Special Warnings and Precautions for Use).

Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose, or whenever possible, as a single morning dose on alternative days. Frequent patient review is required to titrate the dose against disease activity

Acute emergencies

60–80 mg every 4–6 hours for 24 hours, then gradually reduce the dose over several days.

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.

Dosage in special situations

Hydrocortisone replacement therapy

In patients receiving hydrocortisone replacement therapy, the dosage of hydrocortisone should be increased 2 to 4-fold in stressful situations, such as in connection with injuries, infections, or surgical procedures. If necessary, the patient should be switched to parenteral treatment.

Hepatic impairment

The elimination of hydrocortisone may be slower in connection with hepatic diseases, and dose adjustment may be necessary in patients with hepatic impairment.

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindicated in infections including systemic infections where specific anti-infective therapy has not been started.

High doses of corticosteroids impair the immune response to vaccines. Therefore the concomitant administration of live vaccines with corticosteroids should be avoided.

4.4 Special warnings and precautions for use

Adrenal suppression

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months according to the dose and duration of treatment. During prolonged therapy, any intercurrent illness,

trauma or surgical procedure will require a temporary increase in dosage. If corticosteroids have been stopped following prolonged therapy, they may need to be temporarily re-introduced.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimised 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, corticosteroid therapy should be reinstated. If the patient is receiving steroids already, the dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Patients should carry 'steroid treatment' cards, which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage, and the duration of treatment.

Anti-inflammatory / immunosuppressive effects and infection

Suppression of inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation can often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised. New infections may appear during their use.

Corticosteroids may activate latent amoebiasis or strongyloidiasis or exacerbate active disease. Therefore it is recommended that latent or active amoebiasis and strongyloidiasis be ruled out before initiating corticosteroid therapy in any patient at risk of or with symptoms suggestive of either condition.

Caution should be exercised in immunocompromised patients.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children receiving hydrocortisone tablets) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster. If exposed they should seek urgent medical attention. Passive immunisation with *Varicella zoster* immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Live vaccines should not be given to individuals with impaired immune responsiveness caused by high doses of corticosteroids. Killed vaccines or toxoids may be given though their effects may be attenuated.

Corticosteroids should be used with caution in: non-specific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer.

Prolonged use of corticosteroids may produce cataracts, glaucoma with possible damage to the optic nerve, and may enhance the establishment of secondary ocular infections due to fungi or viruses. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible exacerbation of infection and corneal perforation.

Corticosteroid therapy may affect blood coagulation. Caution should be observed in the concomitant use of medicines affecting blood coagulation (such as warfarin or ASA).

Particular care is required when prescribing systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary:

In higher doses, hydrocortisone treatment may increase the prevalence of many acute and latent disease complications and lead to the worsening (or development) of some diseases. Therefore, caution should be exercised in patients with:

a) osteoporosis (postmenopausal females are particularly at risk);
b) hypertension or congestive heart failure;
c) existing or previous history of severe affective disorders (especially previous history of steroid psychosis);
d) diabetes mellitus (or a family history of diabetes);
e) previous history of tuberculosis or characteristic appearance on a chest x-ray. The emergence of active tuberculosis can, however, be prevented by the prophylactic use of anti-tuberculous therapy;
f) glaucoma (or family history or glaucoma);

g) previous corticosteroid-induced myopathy;

h) liver failure;

i) renal insufficiency;

j) epilepsy;

k) peptic ulceration;

l) recent myocardial infarction

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving high doses of corticosteroids may be minimal or absent.

During treatment, the patient should be observed for psychotic reactions, weakness, electrocardiographic changes, hypertension and untoward hormonal effects.

Corticosteroid clearance may be decreased in patients with hypothyroidism and increased in patients with hyperthyroidism.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Children: Corticosteroids cause growth retardation in infancy, childhood and adolescence, this may be irreversible.

Treatment should be limited to the minimum effective dosage in order to minimise suppression of the hypothalamic-pituitary-adrenal axis and growth retardation. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully monitored. (see section 4.2, Posology and method of administration)

Withdrawal symptoms:

In patients who have received more than physiological doses of systemic corticosteroids (approximately 40 mg hydrocortisone) for greater than three weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on

withdrawal of systemic corticosteroids but there is uncertainty about hypothalamic- pituitary adrenal (HPA) suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 30 mg hydrocortisone is reached, dose reduction should be slower to allow the HPA- axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to three weeks is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 160 mg hydrocortisone for three weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be considered even after courses lasting three weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than three weeks
- when a short course has been prescribed within one year of cessation of long- term therapy (months or years)
- patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy
- patients receiving doses of systemic corticosteroid greater than 160 mg hydrocortisone
- patients repeatedly taking doses in the evening.

Patients/and or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see Section 4.8 Undesirable effects). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also Section 4.5 Interaction with other medicinal products and other forms of interaction), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most adverse reactions resolve after either dose reduction or withdrawal of the medicine, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or a previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive ormanic-depressive illness and previous steroid psychosis.

This medicine contains lactose monohydrate. 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

The metabolism of corticosteroids may be enhanced and the therapeutic effects reduced by ephedrine, certain barbiturates (e.g. phenobarbital) and by phenytoin, rifampicin, St John's wort, rifabutin, primidone, carbamazepine and aminoglutethimide. Antiretroviral medicinal products efavirenz and nevirapine, can enhance the metabolic clearance of cortisol, decrease the terminal half-life and thus reduce circulating levels. This may require dose adjustment of hydrocortisone.

Mifepristone may reduce the effect of corticosteroids for 3-4 days.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects. Potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, posaconazole, voriconazole, erythromycin, telithromycin, clarithromycin, ritonavir and grapefruit juice, can inhibit the metabolism of hydrocortisone, and thus increase blood levels.

Ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal (see 4.4 'Special warnings and precautions for use').

Oestrogens and other oral contraceptives increase the plasma concentration of corticosteroids, and dosage adjustments may be required if oral contraceptives are added to or withdrawn from a stable dosage regimen.

The growth promoting effect of somatropin may be inhibited by the concomitant use of corticosteroids.

When used with anticholinesterases, corticosteroids may cause muscle weakness in patients with *myasthenia gravis*.

The desired actions of hypoglycaemic drugs (including insulin), antihypertensives and diuretics are antagonised by corticosteroids.

The effectiveness of coumarin anticoagulants may be affected by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Serum levels of salicylates, such as aspirin and benorilate, may increase considerably if corticosteroid therapy is withdrawn, possibly causing intoxication. Concomitant use of salicylates or of non-steroidal anti-inflammatory drugs (NSAIDs) with corticosteroids increases the risk of gastrointestinal bleeding and ulceration.

The potassium-depleting effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced by corticosteroids and signs of hypokalaemia should be looked for during their concurrent use. The risk of hypokalaemia is increased with theophylline and amphotericin. Corticosteroids should not be given concomitantly with amphotericin, unless required to control reactions.

The risk of hypokalaemia also increases if high doses of corticosteroids are given with high doses of sympathomimetics e.g. bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol and terbutaline. The toxicity of cardiac glycosides, e.g. digoxin, is increased if hypokalaemia occurs.

Concomitant use with methotrexate may increase the risk of haematological toxicity.

The concomitant use of fluoroquinolones and corticosteroid may increase the risk of tendon rupture.

High doses of corticosteroids impair the immune response and so live vaccines should be avoided (see also section 4.4, Special Warnings and Precautions for Use).

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs; however, hydrocortisone readily crosses the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities,

such as cleft palate / lip in man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid states

Breast-feeding

Corticosteroids are excreted in breast milk Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree of adrenal suppression. Mothers taking pharmacological doses of corticosteroids should be advised not to breast-feed. Any maternal treatment should be carefully documented in the infant's medical records to assist in follow up.

Fertility

Patients with adrenal insufficiency have been shown to have reduced parity, which is most likely due to the underlying disease, but there is no indication that hydrocortisone in doses for replacement therapy will affect fertility. Corticosteroids may impair semen quality and cause amenorrhoea.

4.7 Effects on ability to drive and use machines

Hydrocortisone has minor influence on the ability to drive and use machines. In some patients hydrocortisone may cause muscle weakness, muscle atrophy, vertigo, visual field loss, mood changes or psychological instability. Untreated and poorly replaced adrenal insufficiency may affect the ability to drive and use machines.

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamic pituitary- adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see section 4.4, Special Warnings and Precautions for Use).

The following side effects may be associated with the long-term systemic use of corticosteroids.

Blood and lymphatic system disorders:

Leukocytosis

Anti-inflammatory and immunosuppressive effects:

Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, and recurrence of dormant tuberculosis treatment (see section 4.4, Special Warnings and Precautions for Use), allergic reactions, angioneurotic oedema, aggravation of existing infection, activation of latent infection..

Gastrointestinal:

Dyspepsia, peptic ulceration with perforation and haemorrhage, abnormal distension, oesophageal ulceration, candidiasis, acute pancreatitis.

Musculoskeletal:

Proximal myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, muscular atrophy, muscle weakness.

Fluid and electrolyte disturbance:

Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis, increased calcium excretion, negative nitrogen balance due to protein catabolism.

Dermatological:

Impaired healing, skin atrophy, bruising, striae, acne, telangiectasia ecchymosis, petechiae, erythema, increased sweating, allergic dermatitis, urticaria.

Endocrine / metabolic:

Suppression of the hypothalamo-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, development of diabetes, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness)

Neuropsychiatric:

Euphoria, psychological dependence, depression, vertigo, headache, insomnia and aggravation of schizophrenia. Increased intracranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy.

Reproductive system and breast disorders

Menstrual irregularities, amenorrhoea

Ophthalmic:

Increased intra-ocular pressure, exophthalmos, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases, blurred vision with unknown frequency (see also section 4.4).

Cardiovascular:

Myocardial rupture following recent myocardial infarction. Exacerbation of cardiac insufficiency

Vascular:

Hypertension, thromboses

Respiratory, thoracic and mediastinal disorders:

Hiccups

General:

Growth retardation in children, oedema has been reported. Nausea, malaise, increased appetite

Withdrawal symptoms:

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute renal insufficiency, hypotension and death (see section 4.4

Special warnings and precautions for use). A withdrawal syndrome may also occur including fever, asthenia, nausea, increased intracranial pressure, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin modules and weight loss.

Psychiatric disorders:

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdosage may cause nausea and vomiting, sodium and water retention, hyperglycaemia and occasional gastrointestinal bleeding. Treatment need only be symptomatic although cimetidine (200-400 mg by slow intravenous injection every 6 hours) or ranitidine (50 mg by slow intravenous injection every 6 hours) may be administered to prevent gastrointestinal bleeding. 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

ATC Code: H02AB02 Systemic Hormonal Preparations (excluding sex hormones and insulins); Corticosteroids for Systemic Use; Plain; Hydrocortisone.

Hydrocortisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally-occurring and synthetic, which are readily absorbed from the gastro- intestinal tract.

Hydrocortisone is believed to be the principal corticosteroid secreted by the adrenal cortex. Naturally-occurring glucocorticosteroids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. They are also used for their potent anti- inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition they modify the body's immune responses to diverse stimuli.

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 inflammation. They also reduce fibroblast activity and scarring. Glucocorticoids reduce ACTH secretion and suppress the hypothalamic-pituitary-adrenal axis. Hydrocortisone exerts some mineralocorticoid effect. After a 250 mg single dose of hydrocortisone, ACTH secretion is suppressed for approximately 1 to 1.5 days.

5.2 Pharmacokinetic properties

Hydrocortisone is readily absorbed from the gastro-intestinal tract and 90% or more of the drug is reversibly bound to protein.

The binding is accounted for by two protein fractions. One, corticosteroid-binding globulin is a glycoprotein; the other is albumin.

Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol which are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.

The volume of distribution is 0.4–0.7 L/kg. The mean pharmacological half-life of hydrocortisone is 1.5 h, but the biological effect half-life is considerably longer, approximately 10 hours. Hydrocortisone crosses the placental barrier and is excreted in milk in low quantities.

5.3 Preclinical safety data

Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous
Lactose monohydrate
Cellulose, microcrystalline
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/PVDC//aluminium blister packs containing 30 tablets.

Amber coloured glass bottles with white enamelled tin closures containing 50 or 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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