1. NAME OF THE MEDICINAL PRODUCT

Hydventia 10 mg Tablets
Hydrocortisone 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

10mg - Each tablet contains 10 mg of hydrocortisone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

10mg - A white, oval, quarter scored tablet marked ‘F2’ on one side ‘10’ on the reverse. The tablet can be divided into equal halves or quarters.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Corticosteroid

Hydrocortisone Tablets are indicated for:

- use as replacement therapy in primary, secondary, or acute adrenocortical insufficiency. Pre-operatively, and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenocortical reserve.
- replacement therapy in congenital adrenal hyperplasia in children.
- the emergency treatment of severe bronchial asthma, drug hypersensitivity reactions, serum sickness, angioneurotic oedema and anaphylaxis in adults and children.

4.2 Posology and method of administration

Method of Administration

For oral administration.

Posology

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

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.

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

In chronic adrenocortical insufficiency, a dosage of 20 to 30mg a day is usually recommended, sometimes together with 4-6 g of sodium chloride or 50-300 micrograms of fludrocortisone daily.

When immediate support is mandatory, one of the soluble adrenocortical hormone preparations (e.g. dexamethasone sodium phosphate), which may be effective within minutes after parenteral administration, can be life-saving.

Paediatric population: In congenital adrenal hyperplasia the dose should be approximately 0.4 to 0.8mg/kg/day in two or three divided doses, adjusted to the needs of the individual child (see also section 4.4).

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.

Use in serious trauma or illness with known adrenal insufficiency or doubtful adrenocortical reserve

Paediatric population:

Doses are generally higher than that used for chronic adrenocortical insufficiency and should be selected as appropriate for the clinical situation.

All 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.

Pre-operative use

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

Acute emergencies

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

Elderly
Steroids should be used cautiously in the elderly, since adverse effects are enhanced in old age (see section 4.4).

Long term treatment:
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).

4.3 Contraindications

Hydrocortisone Tablets are contraindicated in patients with known hypersensitivity to any of the ingredients. They are also contraindicated in patients with systemic infections (unless specific anti-infective therapy is employed) and in patients vaccinated with live vaccines.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.

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. The patient must be carefully informed how to act in these situations and also advised to immediately seek medical attention should an acute deterioration occur; especially in cases of gastroenteritis, vomiting and/or diarrhoea leading to fluid and salt loss, as well as to inadequate absorption of oral hydrocortisone. If corticosteroids have been stopped following prolonged therapy, they may need to be temporarily re-introduced.

Patients should carry 'Steroid Treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of the 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. Corticosteroids may mask some signs of infection and some serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised. The clinical presentation can often be atypical and there may be an inability to localise

infection in patients on corticosteroids. Corticosteroids may affect the nitroblue tetrazolium test for bacterial infection and produce false negative results. New infections may appear during their use.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpoxshould be advised to avoid close personal contact with chickenpox or herpes zoster and 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 mayneed 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.

Patients with concomitant adrenal insufficiency and retroviral infection, such as HIV, need careful dose adjustment due to potential interaction with antiretroviral medicinal products and increased hydrocortisone dose due to the infection.

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.

During acute adrenal insufficiency parenteral administration of hydrocortisone in high doses, together with sodium chloride 9 mg/ml (0.9%) solution for injection, must be given.

Using higher than normal (supra-physiological) dosages of hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Long-term treatment with higher than physiological hydrocortisone doses can lead to clinical features resembling Cushing´s syndrome with increased adiposity, abdominal obesity, hypertension and diabetes and thus result in an increased risk of cardiovascular morbidity and mortality.

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

- osteoporosis (postmenopausal females are particularly at risk). All glucocorticoids increase calcium excretion and reduce the bone-remodelling rate. Patients with adrenal insufficiency

on long-term glucocorticoid replacement therapy have been found to have reduced bone mineral density;

- hypertension or congestive heart failure;
- recent myocardial infarction;
- existing or previous history of severe affective disorders (especially previous history of steroid psychosis);
- diabetes mellitus (or a family history of diabetes);
- latent tuberculosis, or tuberculin reactivity, close observation is necessary as reactivation may occur. During prolonged corticosteroid therapy, these patients should receive prophylactic use of anti-tuberculoustherapy. The use of hydrocortisone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis.
- glaucoma (or family history or glaucoma). Prolonged use of high doses of glucocorticoids may produce posterior subcapsular cataracts, and glaucoma with possible damage to the optic nerves. Such effects have not been reported in patients receiving replacement therapy with glucocorticoids in doses used in adrenal insufficiency;
- previous corticosteroid-induced myopathy;
- liver failure;
- renal insufficiency, chronic nephritis, acute glomerulonephritis;
- epilepsy;
- peptic ulceration, diverticulitis, fresh intestinal anastomoses
- non-specific ulcerative colitis.
- thrombophlebitis
- exanthematous disease;
- metastatic carcinoma
- myasthenia gravis
- Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

Fat embolism has been reported as a possible complication of hypercortisonism.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

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

A report shows that the use of corticosteroids in cerebral malaria is associated with a prolonged coma and an increased incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions due to

amphotericin. Moreover, there have been cases reported in which concomitant use of amphotericin and hydrocortisone was followed by cardiac enlargement and congestive failure.

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

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.

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

Corticosteroids should be used with caution in patients with hypothyroidism. Patients with adrenal insufficiency should be monitored for thyroid dysfunction as both hypothyroidism and hyperthyroidism may markedly influence the exposure of administered hydrocortisone.

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.

Use in children:

Corticosteroids cause growth retardation in infancy, childhood and adolescence; this may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time (see section 4.2).

Hypertrophic cardiomyopathy was reported after administration of hydrocortisone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

Cerebellar growth impairment has been reported after administration of hydrocortisone to prematurely born infants, therefore the lowest appropriate dosage should be used.

Use in the elderly:

The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life threatening reactions (see section 4.2).

Withdrawal symptoms:

Stopping corticosteroid after prolonged therapy may cause withdrawal symptoms, including fever, myalgia, arthralgia and malaise. In patients who have received more than physiological doses of systemic corticosteroids (approximately 40 mg cortisone or equivalent) for greater than 3 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 HPA-axis suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose equivalent to 40 mg cortisone 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 3 weeks, is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 200 mg daily of cortisone, or equivalent for 3 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 3 weeks or less:

- patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks;
- when a short course has been prescribed within one year of cessation of long term therapy (months or years); patients receiving doses of systemic corticosteroid greater than 200 mg daily of cortisone (or equivalent);
- 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). 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), 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 or manic-depressive illness and previous steroid psychosis.

4.5 Interaction with other medicinal products and other forms of interaction

Potent CYP 3A4 inducers such as phenytoin, rifabutin, primidone, carbamazepine, aminoglutethimide, barbiturates (e.g. phenobarbital), rifampicin, St John's wort and less potent inducers such as the antiretroviral medicinal products efavirenz and nevirapine can enhance the metabolic clearance of cortisol, decrease terminal half-life and thus reduce circulating levels and increase fluctuations of cortisol (due to shorter terminal half-life). This may require dose adjustment of hydrocortisone.

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

Potent CYP 3A4 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. During long-term prophylactic treatment with any of the antibiotics, adjustment of the hydrocortisone dosage should be considered.

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. Interactions of combined oral contraceptives may also apply to combined contraceptive patches.

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

Corticosteroids antagonise the hypoglycaemic effects of hypoglycaemic drugs (including insulin). They antagonise the hypotensive effects of beta-blockers, alpha-blockers, calcium channel blockers,

clonidine, diazoxide, methyldopa, moxonidine, nitrates, nitroprusside, hydralazine, minoxidil, adrenergic neurone blockers, ACE inhibitors and angiotensin II receptor antagonists. Corticosteroids antagonise the effects of diuretics.

Corticosteroids possibly reduce the effects of sodium benzoate and sodium phenyl butyrate.

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. The risk of gastrointestinal bleeding and ulceration increases with concomitant use of salicylates or of non-steroidal anti-inflammatory drugs (NSAIDs), although topical NSAIDs do not generally interact with corticosteroids.

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.

High doses of corticosteroids impair the immune response and so live vaccines should be avoided (see also section 4.4).

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 side-effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs; however, cortisone 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 it is usually resolved 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

Hydrocortisone is excreted in breast milk. Doses of up to 200 mg daily of cortisone are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression but the benefits of breast feeding are likely to outweigh any theoretical risk.

Fertility

Corticosteroids may impair semen quality and cause amenorrhoea.

4.7 Effects on ability to drive and use machines

Steroids such as hydrocortisone may cause fatigue, vertigo, changes to vision and/or muscle weakness. The patient should be advised that if they experience any of these symptoms they should not drive or operate machinery.

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).

Adverse events which have been associated with Hydrocortisone are given below, listed by system organ class and frequency.

Undesirable effects are especially likely to occur at treatment onset or at dose increase.

The undesirable effects are listed below by organ class and the following frequency convention:

Very common: (≥1/10)

Common: (≥1/100 to <1/10)

Uncommon: (≥1/1,000 to <1/100)

Rare: (≥1/10,000 to <1/1,000)

Very rare: (<1/10,000)

Not known (cannot be estimated from the available data).

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

System organ class	**Frequency**	**Undesirable effects**
Infections and infestations	Not known	Gastroenteritis Upper respiratory tract infection Viral infection. Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see section 4.4), activation of fungal and viral infections including herpes
Blood and lymphatic system disorders	Not known	Leukocytosis
Immune system disorders	Not known	Hypersensitivity, anaphylaxis
Endocrine disorders	Not known	Suppression of the hypothalamo-pituitary-adrenal axis Growth retardation in infancy, childhood and

		adolescence. Cushingoid facies Induction of glucose intolerance or diabetes mellitus Impaired carbohydrate tolerance with increased requirement for antidiabetic therapy Increased or decreased motility and number of spermatozoa
Metabolism and nutrition disorders	Not known	Negative protein and calcium balance Sodium and fluid retention Oedema tendency Alkalosis hypokalaemic Hypokalaemia and Increased appetite
Psychiatric disorders (a)	Common	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 disturbance, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia have been reported
Nervous system disorders	Not known	Aggravation of epilepsy Sedation Headache Increased intracranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal
Eye disorders	Not known	Increased intraocular pressure Glaucoma Papilloedema Posterior subcapsular cataracts Corneal or scleral thinning Dry eye

		Exacerbation of ophthalmic viral or fungal diseases Vision blurred (see also section 4.4).
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Myocardial rupture following recent myocardial infarction Congestive heart failure in susceptible patients Hypertrophic cardiomyopathy in prematurely born infants
Vascular disorders	Not known	Hypertension Thromboembolism
Respiratory, thoracic and mediastinal disorders	Not known	Hiccups
Gastrointestinal disorders	Not known	Dyspepsia Peptic ulceration with perforation and haemorrhage Perforation of the small and large bowel particularly in patients with inflammatory bowel disease Deterioration of existing gastric ulcer Abdominal distension Oesophageal ulcer Oesophagitis Upper abdominal pain Tooth erosion Candidiasis Acute pancreatitis and Nausea
Skin and subcutaneous tissue disorders	Not known	Impaired healing Skin atrophy Contusion

		Petechiae and ecchymosis Erythema Skin striae Rash pruritic Cushing-like symptoms Acne Increased sweating Telangiectasia Hirsutism May suppress reactions to skin tests Other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic oedema
Musculoskeletal and connective tissue disorder	Not known	Muscle weakness Loss of muscle mass Proximal myopathy Osteoporosis and spontaneous fractures Vertebral and long bone fractures Avascular osteonecrosis Tendon rupture and Joint swelling
Reproductive system and breast disorders	Not known	Menstruation irregular and amenorrhoea
General disorders and administration site conditions	Not known	Malaise Fatigue
Investigations	Not known	Weight increased High density lipoprotein decreased Blood potassium decreased

(a) 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 and psychological dependence has occurred; the frequency is not known.

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). A withdrawal syndrome may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin modules and weight loss.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Reports of acute toxicity and/or deaths following hydrocortisone overdose are rare. No antidote is available.

Symptoms

Overdosage may cause nausea and vomiting, sodium and water retention, hyperglycaemia and occasional gastrointestinal bleeding.

Management

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: H02A B09.

Pharmacotherapeutic group: Corticosteroids for systemic use, plain, glucocorticoid.

Hydrocortisone is a glucocorticoid and the synthetic form of endogenously produced cortisol. Glucocorticoids are important steroids for intermediary metabolism, immune function, musculoskeletal and connective tissue and the brain. Cortisol is the principal glucocorticoid secreted by the adrenal cortex.

Naturally-occurring glucocorticoids (hydrocortisone and cortisol), which also have salt-retaining properties, are used as replacement therapy in adrenal insufficiency. 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.

5.2 Pharmacokinetic properties

Absorption

Hydrocortisone given by mouth is readily absorbed from the gastrointestinal tract.

Distribution

Hydrocortisone is extensively bound to plasma proteins. In plasma, cortisol is bound to corticosteroid-binding globulin (CBG, also called transcortin) and albumin. The binding is about 90%.

Biotransformation

Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms, such as tetrahydrocortisone and tetrahydrocortisol.

Elimination

Metabolites are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone. Hydrocortisone has a biological half-life of about 100 minutes. Hydrocortisone (cortisol) is a lipophilic drug that is eliminated completely via metabolism with a low clearance and accordingly low intestinal and hepatic extraction ratios.

Hydrocortisone is eliminated completely by metabolism by 11ßHSD type 1 and type 2 enzymes and CYP 3A4 in the liver and in peripheral tissue. CYP 3A4 is involved in the clearance of cortisol by the formation of 6β-hydroxycortisol which is excreted in urine. The transport of cortisol across membranes is expected to be mediated mainly by passive diffusion and therefore renal and biliary clearances are negligible.

Special populations

Renal impairment

A small amount of cortisol is excreted in the urine unchanged (<0.5% of the daily production), meaning that cortisol is eliminated completely by metabolism. Since severe renal impairment may affect medicinal products completely eliminated via metabolism, dose adjustment may be needed.

Hepatic impairment

No study has been performed in patients with hepatic impairment, however data in the literature for hydrocortisone support that no dose adjustment is required in mild to moderate hepatic impairment. In case of severe hepatic impairment, the functional liver mass decreases and thus the metabolising capacity for hydrocortisone. This may require dose individualisation.

Paediatric population

No pharmacokinetic data are available in children or adolescents.

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

Prosolv 90 (silicified microcrystalline cellulose)

Magnesium stearate

Talc

Sodium starch glycolate

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister strips comprising aluminium foil and opaque white film (PVC/PVdC, PVC/PVdC/PVC or PVC/PE/PVdC).

The blister strips are packed in cartons of 30 tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Resolution Chemicals Ltd.,
Wedgwood Way,
Stevenage, Herts,
SG1 4QT, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 10321/0204

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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