HYDROCORTISONE 10MG TABLETS
PL 17507/0054

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UKPAR

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LAY SUMMARY

The MHRA granted Auden Mckenzie Ltd Marketing Authorisations (licences) for the medicinal products Hydrocortisone 10mg Tablets (PL 17507/0054) and Hydrocortisone 20mg Tablets (PL 17507/0055). These are prescription only medicines (POM) to be taken when your body is not making enough hydrocortisone, either because part of the adrenal gland is not working or because surgery, injuries or other stressful events.

Hydrocortisone 10mg and 20mg Tablets contain the active ingredient hydrocortisone which is a synthetic version of the hormone hydrocortisone, which is important for many body functions.

The test products were considered to be equivalent to the reference products Hydrocortone 10mg and 20mg Tablets (Merck Sharpe & Dohme Ltd) based on the data submitted.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Hydrocortisone 10mg and 20mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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HYDROCORTISONE 20MG TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Hydrocortisone 10mg and 20mg Tablets to Auden Mckenzie Ltd on 18 May 2007. The products are prescription only medicines.

Two strengths of hydrocortisone were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC as amended, claiming to be generic products of Hydrocortone 10mg and 20mg Tablets (Merck Sharp & Dohme). The reference products have been authorised in the UK since February 1989 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient hydrocortisone and are indicated for use as replacement therapy in primary, secondary or acute adrenocortical insufficiency as well as pre-operatively and during serious trauma or illness in patients with known adrenal insufficiency or doubtful adrenocortical reserve.

Hydrocortisone is a corticosteroid with both glucocorticoid and, to a lesser extent, mineralocorticoid activity. Glucocorticoids cause profound and varied metabolic effects. In addition they modify the body's immune responses to diverse stimuli.

Both applications were submitted at the same time and depend on the bioequivalence study that compares the applicant’s products with the reference product Hydrocortone 20mg Tablets (Merck Sharpe & Dohme Ltd). Consequently, all sections of the Scientific Discussion refer to both applications.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The products are formulated as tablets containing 10mg or 20mg of the active pharmaceutical ingredient hydrocortisone. The excipients present are maize starch, lactose monohydrate, povidone, colloidal anhydrous silica, talc and magnesium stearate.

Hydrocortisone 10mg and 20mg Tablets are presented in aluminium-foil sealed PVC blisters in packs of 30 tablets.

DRUG SUBSTANCE

Hydrocortisone

All aspects of the manufacture and control of hydrocortisone are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of hydrocortisone for inclusion in this medicinal product.

Stability data have been generated supporting a retest period of 3 years when stored in the proposed packaging, protected from light.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in its production is sourced from healthy animals under the same conditions as that for human consumption.

Dissolution Profiles

Dissolution profiles for the drug product (Hydrocortisone 20mg Tablets) were found to be similar to the reference product (Hydrocortone 20mg Tablets, Merck Sharp & Dohme Ltd) in water and 0.1M HCl.

Impurity Profiles

The impurity profiles for two batches of the drug product (Hydrocortisone 20mg Tablets) and reference product (Hydrocortone 20mg Tablets, Merck Sharp & Dohme Ltd) were comparable.

Manufacture

A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of both strengths. The results are satisfactory.

Finished product specification
The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. A dissolution test has been included in the specification since hydrocortisone is a polymorph, and there can be variations in solubility. Batch analysis data have demonstrated compliance with the proposed release specification. The applicant commits to submitting supplementary batch analysis data when additional batches of the drug substance are available. Suitable reference standards were used.

Container Closure System
Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability data support the proposed shelf-life of 2 years with storage conditions “Keep blister in the outer carton.”

Bioequivalence/bioavailability
Refer to the clinical assessment report.

SPC, PIL and Labels
The SPC and labels are pharmaceutically acceptable.

A patient information leaflet (PIL) has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act on the information that it contains.

CONCLUSION

The proposed products have been shown to be generic products of the reference products and have met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution and impurity profiles have been demonstrated for the proposed and reference products.

It is recommended that Marketing Authorisations should be granted for these applications.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

These are generic abridged applications for tablets containing 10mg and 20mg hydrocortisone.

The applications were submitted under the provisions of Directive 2001/83/EC Article 10.1 as amended, claiming that Hydrocortisone 10mg and 20mg Tablets are generic products of Hydrocortone 10mg and 20mg Tablets (Merck Sharp & Dohme Ltd) which were authorised in the UK in February 1989.

Hydrocortisone is a corticosteroid with predominantly glucocorticoid actions. Corticosteroids are potent anti-inflammatory compounds and in oral form are used to treat numerous autoimmune and inflammatory conditions including asthma, bursitis, Crohn's disease, Ulcerative colitis and others. They are also used to treat severe allergic reactions and to prevent rejection after organ transplant. Corticosteroids are also used therapeutically in physiological doses for replacement therapy in adrenal insufficiency.

INDICATIONS

The following indications have been approved:

> 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.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for these products to be used for the above indications are consistent with those for the reference product.

PHARMACOKINETICS

No new data were submitted. The pharmacokinetics of hydrocortisone are well described. Hydrocortisone is readily absorbed from the gastrointestinal tract and peak blood concentrations are attained in approximately one hour. The plasma half-life is approximately 100 minutes. It is more than 90% bound to plasma proteins. Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol. These are excreted in the urine mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone.

BIOEQUIVALENCE

A single bioequivalence study was presented for the higher 20mg strength. The applicant has not provided evidence of linearity of the two doses, but in accordance with CPMP guidelines on bioavailability and bioequivalence, the fact that the applicant has conducted the study on the higher strength is acceptable.

A comparative two-treatment, two-sequence, two-period, single-dose crossover study in 28 healthy fasted male volunteers was conducted in compliance with Good Clinical Practice (GCP). The subjects were randomised to receive 20mg orally of either the applicant's 20mg test product or the reference product, Hydrocortone 20mg Tablets (Merck Sharp & Dohme Ltd, UK). Serum drug levels were monitored for 24 hours following dosing. This was sufficient to meet the 80% criterion for AUC_t/AUC_{inf}. The schedule was appropriate for accurate determination of AUC_{inf} and C_{max}. The mean elimination half life was 2h, therefore the washout period between phases was sufficiently long at 7 days.

The randomisation scheme was balanced for sequence and appears random.
Data for AUC_t, AUC_{inf} and C_{max} were log-transformed and analysed by ANOVA.

Results

Thirty subjects were enrolled in the study and dosed in the first period. Twenty-eight subjects completed the study and their samples were analysed (two subjects were withdrawn from the study in the first period due to adverse events (vasovagal attack, pyrexia) following dosing and their samples were not analysed).

Bioequivalence results for log-transformed test/reference ratios with 90% confidence intervals are presented below:

Test parameter	Test product (geometric means) (CV%)	Reference product (geometric means) (CV%)	Ratio of means (%)	90% CI	Intra-subject CV (%)
AUC_{0-t} (ng.h/ml)	773.247 (36.5)	743.519 (34.3)	103.2	95.3-111.75	17.6
AUC_{0-inf} (ng.h/ml)	908.881 (34.4)	917.757 (35.7)	99.4	90.76-108.92	20.2
C_{max} ng/ml	274.490 (26.3)	270.671 (28.7)	102.1	91.68-113.73	23.9
T_{max} (h)	1.16	1.07			

Bioequivalence of the test product with Hydrocortone 20mg Tablets has been satisfactorily demonstrated in accordance with CPMP criteria.

PHARMACODYNAMICS

No new data submitted. The pharmacodynamics of hydrocortisone are well described. Hydrocortisone is synthesised in the body by the adrenal cortex, and is under regulatory control from the hypothalamus and pituitary, via the releasing hormones corticorelin and corticotrophin or ACTH. In return, the glucocorticoids, such as hydrocortisone, act to inhibit production and release of these releasing hormones by a negative feedback mechanism (hypothalamic-pituitary-adrenal HPA axis).

In instances of adrenal insufficiency, corticosteroids are used in physiological doses for replacement therapy. The approximate equivalent dose of hydrocortisone, in terms of its glucocorticoid properties alone is 20 mg.

CLINICAL EFFICACY

No new efficacy data were presented in these applications and none are required.

CLINICAL SAFETY

No formal safety data were presented in these applications and none are required.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

The clinical efficacy and safety of hydrocortisone is well known from its extensive use in clinical practice. No new data were submitted and this is acceptable. Bioequivalence of the product has been shown. Considering the relative composition of the 10mg and 20mg products, dissolution profiles and hydrocortisone pharmacokinetics, extrapolation of the outcome of the bioequivalence study to the lower strength product is justified. Marketing Authorisations should be granted for these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Hydrocortisone 10mg and 20mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Hydrocortisone 20mg Tablets and Hydrocortone 20mg Tablets (Merck Sharp & Dohme Ltd).

No new or unexpected safety concerns arise from these applications.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the reference products are interchangeable. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 24 October 2005.

2 Following standard checks and communication with the applicant, the MHRA considered the applications valid on 08 November 2005.

3 Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 30 November 2005, 13 December 2005 and 07 February 2007 and further information relating to the clinical dossiers on 21 July 2006.

4 The applicant responded to the MHRA's requests, providing further information on 20 October 2006, 12 February 2007 and 30 March 2007 for the quality sections, and again on 05 February 2007 for the clinical sections.

5 The applications were determined on 18 May 2007.

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STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydrocortisone 10mg

Excipients:

Hydrocortisone 10mg Tablets contain 64.3mg lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Round, white tablet, with ‘H10’ imprinted on one side and a breakline on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Corticosteroid.

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.

4.2 Posology and method of administration

Dosage must be individualised according to the response of the individual patient. The lowest possible dosage should be used. Doses should be multiples of 10 (ie 10mg, 20mg, 30mg, etc).

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 (eg 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 4.4 'Special warnings and precautions for use').

In chronic adrenocortical insufficiency, a dosage of 20 to 30mg a day is usually recommended, sometimes together with 4-6g of sodium chloride or 50-300micrograms of fludrocortisone daily. When immediate support is mandatory, one of the soluble adrenocortical hormone preparations (eg dexamethasone sodium phosphate), which may be effective within minutes after parenteral administration, can be life-saving.

Use in children: 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.

Use in the elderly: 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. Close supervision is recommended particularly when on long term treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Systemic fungal infections.

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

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.

The lowest possible dosage of corticosteroids should be used and when reduction in dosage is possible, the reduction should be gradual.

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.

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.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Average and large dosages of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increase excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

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

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation may occur. During prolonged corticosteroid therapy, these patients should receive prophylactic chemotherapy.

The use of hydrocortisone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis.

Corticosteroids should be used with caution in renal insufficiency, hypertension, diabetes or in those with a family history of diabetes, congestive heart failure, thrombophlebitis, exanthematous disease, chronic nephritis, acute glomerulonephritis, metastatic carcinoma, osteoporosis (postmenopausal patients are at special risk), severe affective disorders (particularly if there is a history of steroid-induced psychosis), epilepsy, previous steroid myopathy, glaucoma (or family history of glaucoma), myasthenia gravis, non-specific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer. Signs of peritoneal irritation following gastro-intestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent.

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

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

Prolonged courses of corticosteroids increase susceptibility to infections and their severity. The clinical presentation of infections may also be atypical.

Corticosteroids may mask some signs of infection and some serious infection such as septicaemia and tuberculosis may reach an advanced stage before being recognised. There may be an inability to localise infection in patients on corticosteroids. Corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false negative results.

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.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, 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 corneal perforation.

Corticosteroids may increase or decrease motility and number of spermatozoa.

Diabetes may be aggravated, necessitating a higher insulin dosage. Latent diabetes mellitus may be precipitated.

Menstrual irregularities may occur, and this possibility should be mentioned to female patients.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroids, especially when a patient has a history of drug allergies.

Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinaemia.

Withdrawal: Drug-induced secondary adrenocortical insufficiency may result from too rapid a 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 (see 4.5 'Interaction with other medicinal products and other forms of interactions').

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 30 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.

Children: Corticosteroids cause growth retardation in infancy, childhood and adolescence. Treatment should be limited to the minimum 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is an increased risk of hypokalaemia when corticosteroids are given with amphotericin. Avoid concomitant use unless amphotericin is needed to control reactions.

Corticosteroids antagonise the effects of diuretics. There is an increased risk of hypokalaemia when corticosteroids are given with loop diuretics, thiazides and related diuretics. There is also an increased risk of hypokalaemia when corticosteroids are given with acetazolamide, or cardiac glycosides, or theophylline or high doses of $beta_2$ sympathomimetics

Corticosteroids can antagonize the hypotensive effects of ACE inhibitors, adrenergic neurone blockers, alpha-blockers, angiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, hydralazine, methyldopa, minoxidil, moxonidine, nitrates, or nitroprusside.

The metabolism of corticosteroids can be accelerated resulting in decreased blood levels and lessened physiological activity by aminoglutethimide, barbiturates, carbamazepine, ephedrine, phenytoin, primidone, rifabutin, or rifampicin. Adjustment of the corticosteroid dosage may be required.

The effect of corticosteroids may be reduced for 3 - 4 days after mifepristone.

Corticosteroids may enhance or reduce the anticoagulant effect of coumarins. The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although high-dose corticosteroids may enhance the anticoagulant effect.

The metabolism of corticosteroids can be inhibited by erythromycin, although not when small amounts of erythromycin are used topically.

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

The plasma concentration of corticosteroids is increased by oral contraceptives containing oestrogens. Interactions of combined oral contraceptives may also apply to combined contraceptive patches. In the case of hormone replacement therapy, low doses are unlikely to induce interactions. The plasma concentration of corticosteroids may possibly be increased by ritonavir.

Corticosteroids may inhibit the growth-promoting effect of somatropin.

Corticosteroids antagonise the hypoglycaemic effect of antidiabetics.

There is an increased risk of haematological toxicity when corticosteroids are given with methotrexate.

Corticosteroids may reduce the effects of sodium benzoate and of sodium phenylbutyrate.

There is an increased risk of gastro-intestinal bleeding and ulceration when corticosteroids are given with aspirin or NSAIDs, although topical NSAIDs do not generally interact with corticosteroids. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia.

Moreover, corticosteroids may affect the nitroblue tetrazolium test for bacterial infection and produce false negative results.

4.6 Pregnancy and lactation

Studies in animals have shown reproductive toxicity (see section 5.3). There is no evidence in humans that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip. However, there may be an increased risk of intra-uterine growth retardation when corticosteroids are administered for prolonged periods or repeatedly during pregnancy. Patients with pre-eclampsia or fluid retention require close monitoring.

As with all medicinal products corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important.

Corticosteroids are found in breast milk.

Infants born of mothers who have received substantial doses of corticosteroids during pregnancy or during breast feeding should be carefully observed for signs of hypoadrenalism. Maternal treatment should be carefully documented in the infant's medical records to assist in follow up.

4.7 Effects on ability to drive and use machines

Hydrocortisone may cause vertigo, visual field loss and muscle wasting and weakness. If affected, patients should not drive or operate machinery (see also section 4.8).

4.8 Undesirable effects

Blood and the lymphatic system disorders: Leucocytosis.

Endocrine disorders: Development of Cushingoid state, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), manifestations of latent diabetes mellitus.

General disorders: Hypersensitivity, malaise.

Metabolism and nutrition disorders: Negative nitrogen balance due to protein catabolism, weight gain, increased appetite.

Nervous system disorders: Convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment, vertigo, headache, psychic disturbances, psychological dependence, insomnia.

Eye disorders: Posterior subcapsular cataracts, increased intra-ocular pressure, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease, glaucoma, exophthalmos.

Cardiovascular disorders: Myocardial rupture following recent myocardial infarction (see 4.4 'Special warnings and precautions for use'), fluid retention, congestive heart failure in susceptible patients, hypertension, thromboembolism.

Gastrointestinal disorders: Peptic ulcer with possible perforation and haemorrhage, perforation of the small and large bowel particularly in patients with inflammatory bowel disease, pancreatitis, abdominal distension, ulcerative oesophagitis, dyspepsia, oesophageal candidiasis, nausea.

Skin and subcutaneous tissue disorder: Impaired wound healing, thin fragile skin, petechiae, and ecchymoses, erythema, striae, telangiectasia, acne, increased sweating, may suppress reactions to skin tests, other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic oedema, hirsutism.

Musculoskeletal, connective tissue and bone disorders: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis (especially in post-menopausal females), vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture.

Reproductive system and breast disorders: Increased or decreased motility and number of spermatozoa, menstrual irregularities, amenorrhoea,

Respiratory disorders: Hiccups.

Investigations: Sodium retention, potassium loss, hypokalaemic alkalosis, increased calcium excretion, decreased carbohydrate tolerance, hyperglycemia,

4.9 Overdose

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. No antidote is available. Treatment is probably not indicated for reactions due to chronic poisoning unless the patient has a condition that would render him/her unusually susceptible to ill effects from corticosteroids. In this case, symptomatic treatment should be instituted as necessary.

Anaphylactic and hypersensitivity reactions may be treated with adrenaline, positive-pressure artificial respiration and aminophylline. The patient should be kept warm and quiet.

The biological half-life of hydrocortisone is about 100 minutes.

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.

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.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Povidone K90
Silica, colloidal anhydrous
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Keep blister in the outer carton.

6.5 Nature and contents of container

PVC/aluminium blister containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Auden Mckenzie (Pharma Division) Ltd
Unit 30 Stadium Business Centre
North End Road
Wembley
Middlesex
HA9 0AT

8 MARKETING AUTHORISATION NUMBER(S)

PL 17507/0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/05/2007

10 DATE OF REVISION OF THE TEXT

18/05/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydrocortisone 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydrocortisone 20mg

Excipients:

Hydrocortisone 20mg Tablets contain 128.6mg lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Round, white tablet, with ‘H20’ imprinted on one side and a breakline on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Corticosteroid.

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.

4.2 Posology and method of administration

Dosage must be individualised according to the response of the individual patient. The lowest possible dosage should be used. Doses should be multiples of 10 (ie 10mg, 20mg, 30mg, etc).

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 (eg 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 4.4 'Special warnings and precautions for use').

In chronic adrenocortical insufficiency, a dosage of 20 to 30mg a day is usually recommended, sometimes together with 4-6g of sodium chloride or 50-300micrograms of fludrocortisone daily. When immediate support is mandatory, one of the soluble adrenocortical hormone preparations (eg dexamethasone sodium phosphate), which may be effective within minutes after parenteral administration, can be life-saving.

Use in children: 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.

Use in the elderly: 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. Close supervision is recommended particularly when on long term treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Systemic fungal infections.

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

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.

The lowest possible dosage of corticosteroids should be used and when reduction in dosage is possible, the reduction should be gradual.

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.

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.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Average and large dosages of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increase excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

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

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation may occur. During prolonged corticosteroid therapy, these patients should receive prophylactic chemotherapy.

The use of hydrocortisone tablets in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis.

Corticosteroids should be used with caution in renal insufficiency, hypertension, diabetes or in those with a family history of diabetes, congestive heart failure, thrombophlebitis, exanthematous disease, chronic nephritis, acute glomerulonephritis, metastatic carcinoma, osteoporosis (postmenopausal patients are at special risk), severe affective disorders (particularly if there is a history of steroid-induced psychosis), epilepsy, previous steroid myopathy, glaucoma (or family history of glaucoma), myasthenia gravis, non-specific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer. Signs of peritoneal irritation following gastro-intestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent.

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

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

Prolonged courses of corticosteroids increase susceptibility to infections and their severity. The clinical presentation of infections may also be atypical.

Corticosteroids may mask some signs of infection and some serious infection such as septicaemia and tuberculosis may reach an advanced stage before being recognised. There may be an inability to localise infection in patients on corticosteroids. Corticosteroids may affect the nitrobluetetrazolium test for bacterial infection and produce false negative results.

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.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, 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 corneal perforation.

Corticosteroids may increase or decrease motility and number of spermatozoa.

Diabetes may be aggravated, necessitating a higher insulin dosage. Latent diabetes mellitus may be precipitated.

Menstrual irregularities may occur, and this possibility should be mentioned to female patients.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroids, especially when a patient has a history of drug allergies.

Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinaemia.

Withdrawal: Drug-induced secondary adrenocortical insufficiency may result from too rapid a 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 (see 4.5 'Interaction with other medicinal products and other forms of interactions').

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 30 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.

Children: Corticosteroids cause growth retardation in infancy, childhood and adolescence. Treatment should be limited to the minimum 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is an increased risk of hypokalaemia when corticosteroids are given with amphotericin. Avoid concomitant use unless amphotericin is needed to control reactions.

Corticosteroids antagonise the effects of diuretics. There is an increased risk of hypokalaemia when corticosteroids are given with loop diuretics, thiazides and related diuretics. There is also an increased risk of hypokalaemia when corticosteroids are given with acetazolamide, or cardiac glycosides, or theophylline or high doses of $beta_2$ sympathomimetics

Corticosteroids can antagonize the hypotensive effects of ACE inhibitors, adrenergic neurone blockers, alpha-blockers, angiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, hydralazine, methyldopa, minoxidil, moxonidine, nitrates, or nitroprusside.

The metabolism of corticosteroids can be accelerated resulting in decreased blood levels and lessened physiological activity by aminoglutethimide, barbiturates, carbamazepine, ephedrine, phenytoin, primidone, rifabutin, or rifampicin. Adjustment of the corticosteroid dosage may be required.

The effect of corticosteroids may be reduced for 3 - 4 days after mifepristone.

Corticosteroids may enhance or reduce the anticoagulant effect of coumarins. The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although high-dose corticosteroids may enhance the anticoagulant effect.

The metabolism of corticosteroids can be inhibited by erythromycin, although not when small amounts of erythromycin are used topically.

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

The plasma concentration of corticosteroids is increased by oral contraceptives containing oestrogens. Interactions of combined oral contraceptives may also apply to combined contraceptive patches. In the case of hormone replacement therapy, low doses are unlikely to induce interactions. The plasma concentration of corticosteroids may possibly be increased by ritonavir.

Corticosteroids may inhibit the growth-promoting effect of somatropin.

Corticosteroids antagonise the hypoglycaemic effect of antidiabetics.

There is an increased risk of haematological toxicity when corticosteroids are given with methotrexate.

Corticosteroids may reduce the effects of sodium benzoate and of sodium phenylbutyrate.

There is an increased risk of gastro-intestinal bleeding and ulceration when corticosteroids are given with aspirin or NSAIDs, although topical NSAIDs do not generally interact with corticosteroids. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia.

Moreover, corticosteroids may affect the nitroblue tetrazolium test for bacterial infection and produce false negative results.

4.6 Pregnancy and lactation

Studies in animals have shown reproductive toxicity (see section 5.3). There is no evidence in humans that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip. However, there may be an increased risk of intra-uterine growth retardation when corticosteroids are administered for prolonged periods or repeatedly during pregnancy. Patients with pre-eclampsia or fluid retention require close monitoring.

As with all medicinal products corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important.

Corticosteroids are found in breast milk.

Infants born of mothers who have received substantial doses of corticosteroids during pregnancy or during breast feeding should be carefully observed for signs of hypoadrenalism. Maternal treatment should be carefully documented in the infant's medical records to assist in follow up.

4.7 Effects on ability to drive and use machines

Hydrocortisone may cause vertigo, visual field loss and muscle wasting and weakness. If affected, patients should not drive or operate machinery (see also section 4.8).

4.8 Undesirable effects

Blood and the lymphatic system disorders: Leucocytosis.

Endocrine disorders: Development of Cushingoid state, suppression of growth in children, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), manifestations of latent diabetes mellitus.

General disorders: Hypersensitivity, malaise.

Metabolism and nutrition disorders: Negative nitrogen balance due to protein catabolism, weight gain, increased appetite.

Nervous system disorders: Convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment, vertigo, headache, psychic disturbances, psychological dependence, insomnia.

Eye disorders: Posterior subcapsular cataracts, increased intra-ocular pressure, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease, glaucoma, exophthalmos.

Cardiovascular disorders: Myocardial rupture following recent myocardial infarction (see 4.4 'Special warnings and precautions for use'), fluid retention, congestive heart failure in susceptible patients, hypertension, thromboembolism.

Gastrointestinal disorders: Peptic ulcer with possible perforation and haemorrhage, perforation of the small and large bowel particularly in patients with inflammatory bowel disease, pancreatitis, abdominal distension, ulcerative oesophagitis, dyspepsia, oesophageal candidiasis, nausea.

Skin and subcutaneous tissue disorder: Impaired wound healing, thin fragile skin, petechiae, and ecchymoses, erythema, striae, telangiectasia, acne, increased sweating, may suppress reactions to skin tests, other cutaneous reactions such as allergic dermatitis, urticaria, angioneurotic oedema, hirsutism.

Musculoskeletal, connective tissue and bone disorders: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis (especially in post-menopausal females), vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathological fracture of long bones, tendon rupture.

Reproductive system and breast disorders: Increased or decreased motility and number of spermatozoa, menstrual irregularities, amenorrhoea,

Respiratory disorders: Hiccups.

Investigations: Sodium retention, potassium loss, hypokalaemic alkalosis, increased calcium excretion, decreased carbohydrate tolerance, hyperglycemia,

4.9 Overdose

Reports of acute toxicity and/or deaths following overdosage with glucocorticoids are rare. No antidote is available. Treatment is probably not indicated for reactions due to chronic poisoning unless the patient has a condition that would render him/her unusually susceptible to ill effects from corticosteroids. In this case, symptomatic treatment should be instituted as necessary.

Anaphylactic and hypersensitivity reactions may be treated with adrenaline, positive-pressure artificial respiration and aminophylline. The patient should be kept warm and quiet.

The biological half-life of hydrocortisone is about 100 minutes.

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.

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.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Povidone K90
Silica, colloidal anhydrous
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Keep blister in the outer carton.

6.5 Nature and contents of container

PVC/aluminium blister containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Auden Mckenzie (Pharma Division) Ltd
Unit 30 Stadium Business Centre
North End Road
Wembley
Middlesex
HA9 0AT

8 MARKETING AUTHORISATION NUMBER(S)

PL 17507/0055

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/05/2007

10 DATE OF REVISION OF THE TEXT

18/05/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Hydrocortisone 10 mg and 20 mg Tablets

Before this product is used, please read this leaflet carefully as it contains important information. Do not throw it away. You may want to read it again. If you have any further questions, please ask your doctor or pharmacist (chemist).
This product has been prescribed for you. You should not pass it on to other people. It may harm them.

In this leaflet:

1. Why do you need to take this medicine?

Your doctor has prescribed Hydrocortisone Tablets for you because your body is not making enough hydrocortisone, either because part of the adrenal gland is not working or because of surgery, injuries or other stressful events. Hydrocortisone is one of the body's natural steroid hormones, produced by the adrenal gland; it is important for many body functions.

2. How does this medicine work?

Hydrocortisone Tablets are known as corticosteroids ('steroids'). The tablets are a synthetic version of the hormone hydrocortisone, made naturally by the body.

3. Before you take Hydrocortisone Tablets

Do not take Hydrocortisone Tablets if:

- you think that you may have had an allergic, or any other type of, reaction to Hydrocortisone Tablets or a similar medicine in the past. An allergic reaction may be recognized as a rash, itching, swollen face or lips, or shortness of breath
- you have thrush, Candida or any other fungal infection
- you are going to have any vaccinations – you must tell the doctor or nurse that you have been prescribed Hydrocortisone Tablets.

Are you pregnant or breast feeding?

Tell the doctor if you are pregnant, think you might be pregnant or are trying to become pregnant. Hydrocortisone Tablets can reach your baby and may slow its growth.

Small amounts of hydrocortisone may get into breast milk; tell your doctor if you are breast feeding.

Other things to do or know before you take the tablets

If the answer to any of the following questions is '**Yes**', you may still be able to take Hydrocortisone Tablets, but you should discuss this with your doctor before taking the tablets:

- Have you recently had a heart attack?
- Do you have tuberculosis (TB), or have had TB in the past?
- Do you have a stomach ulcer, or other digestive problems?
- Do you have chicken pox, shingles, or a herpes infection in your eye(s)?

- Have you had muscle weakness after using steroids in the past?
- Have you recently visited a tropical country?

You should also tell your doctor before taking the tablets if you have, or have had in the past, any of the following problems:
- diabetes (or if there is a history of diabetes in your family)
- heart problems
- thrombophlebitis (swelling and redness along a vein which is extremely tender when touched)
- exanthematous disease (disease affecting the skin, rash)
- metastatic carcinoma (cancer that has spread from one part of the body to another)
- high blood pressure
- glaucoma - increased pressure in the eye (or if there is a history of glaucoma in your family)
- kidney or liver disease
- myasthenia gravis (a condition affecting the muscles)
- osteoporosis (brittle bones)
- mood disorders
- epilepsy
- thyroid problems.

This medicine contains **lactose**. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

IMPORTANT!

If you are taking or have recently (within the last 3 months) been taking Hydrocortisone Tablets and **you become ill, suffer stress, get injured or are about to have surgery**, tell your doctor or other healthcare professional. Your dose of Hydrocortisone Tablets may need to be increased (or you may have to start taking it again for a short time) to prevent a sharp fall in blood pressure.

If you have been on Hydrocortisone Tablets for longer than 3 weeks and wish to stop taking it, **do not stop suddenly** as you could have a severe drop in blood pressure which could kill you.

Taking Hydrocortisone Tablets for a long time increases your chance of getting infections and these might be worse than normal. Also, hydrocortisone treatment can hide the usual symptoms of infection. Amoebic dysentery and an infestation of a gut worm (*strongyloidiasis*) may be activated or become worse, as may fungal and viral infections of the eye.

It is particularly important to **avoid contact** with people who have **chicken pox** or **shingles,** especially if you have not already had these illnesses or are not sure if you have had them. Hydrocortisone Tablets increase the risk of a severe bout of chicken pox. You should still take your Hydrocortisone Tablets, but the dose may need adjusting. If you are about to take hydrocortisone, or are already taking it, and you get a rash or other symptoms of an infection, **tell your doctor immediately**.

Taking other medicines

Always tell your doctor if you are taking any other medicines (including those you bought yourself without a prescription) because taking some medicines together with Hydrocortisone Tablets can be harmful.

You should tell your doctor if you are taking any of the following medicines, as they can affect the way the tablets work:

- **amphotericin or ketoconazole** (certain medicines used to treat fungal infections)
- **diuretics** (water tablets)
- **acetazolamide** (a medicine used to treat glaucoma)
- **cardiac glycosides** (medicines used to treat heart failure)
- **theophylline and beta$_2$ sympathomimetics** (medicines used to treat asthma)
- **angiotensin-converting enzyme (ACE) inhibitors, adrenergic neurone blockers, alpha-blockers, angiotensin-II receptor agonists, beta-blockers, calcium-channel**

blockers, nitrates, nitroprusside, clonidine, diazoxide, hydralazine, methyldopa, minoxidil and moxonidine (medicines used to treat high blood pressure and/or heart conditions)
- **aminoglutethimide** (a medicine used in the treatment of cancer)
- **barbiturates, phenytoin, primidone and carbamazepine** (medicines used to treat epilepsy)
- **ephedrine** (a decongestant for a blocked nose)
- **rifabutin** or **rifampicin** (antibiotics used for TB)
- **mifepristone** (a drug used to assist medical termination of pregnancy)
- **anticoagulants** (medicines that thin the blood)
- **erythromycin** (a medicine used to treat bacterial infections)
- oral contraceptive (the 'pill') or contraceptive patch
- **ritonavir** (a medicine used in the treatment of HIV infections)
- **somatropin** (a growth hormone)
- medicines used to treat diabetes
- **methotrexate** (a medicine used to treat rheumatoid arthritis)
- **sodium benzoate and sodium phenylbutyrate** (medicines used to treat urea cycle disorders)
- **aspirin** and **other non-steroidal anti-inflammatory medicines (NSAIDs)** (medicines used to treat mild to moderate pain).

Hydrocortisone Tablets could affect the results of some tests performed by your doctor or in hospital, so tell your doctor or nurse that you are taking these tablets before any tests are carried out.

Driving and using machines Medicines like Hydrocortisone Tablets may cause vertigo (a spinning sensation), changes in vision and/or muscle weakness. If you are affected in this way, do not drive or operate machines.

4. How to take Hydrocortisone Tablets

Remember always to carry a Steroid Treatment Card. Make sure your doctor or pharmacist gives you this and has filled out the details including the dose and how long you will have treatment.

Take the tablets by mouth, exactly as your doctor, pharmacist or medicine label tells you to. To help you remember to take the tablets, it is best to take them at the same time each day, with or without a meal.

If you have surgery, an accident or become unwell while taking the tablets, tell whoever is treating you that you are taking Hydrocortisone Tablets.

The usual dose is as follows:

Adults:
20 to 30 mg a day, sometimes taken together with 4 to 6 g of sodium chloride or 50 to 300 micrograms of fludrocortisone. Doses will be usually be multiples of 10 (eg 10 mg, 20 mg, 30 mg, etc).

Your doctor may want to prescribe more. The exact dose depends upon your condition.

Elderly:
Your doctor may want to see you more regularly to check how you are getting on with the tablets.

Children:
0.4 to 0.8 mg a day for every kilogram the child weighs, in 2 or 3 separate doses. Your doctor will prescribe the lowest dose that is effective for the child, and will keep an eye on their growth and development.

If you have been on hydrocortisone for at least 3 weeks and you no longer need to take it, **do not stop taking the tablets suddenly**. Your dose will be reduced gradually.

If you forget a dose:
Wait and take the next one as normal. Do not take a dose to make up.

If you take too many tablets:
Contact your doctor or pharmacist as soon as possible.

5. Possible side effects

Like all steroids, these tablets may cause side effects, although not everyone gets them. If you are taking replacement steroids like these, you should be less likely to get side effects than people taking steroids for other illnesses.

Blood and lymphatic system: Increased number of white blood cells.

Endocrine: Development of 'Cushingoid' state (cheeks and stomach increase in size; limbs become thin, with flushed face and increased appetite); stunted growth in children; failure of the adrenal and pituitary glands to produce hormones, particularly after surgery, an accident or illness.

General: Allergic (hypersensitivity) reactions, which can include rash, wheals, swelling of hands, feet, face and difficulty with breathing; contact your doctor immediately if any of these occur.
General feeling of illness (malaise).

Metabolism and nutrition: Weight gain; increased appetite.

Nervous system: Fits (convulsions); spinning sensation (vertigo); headache (sometimes severe); changes of mood; psychological dependence; trouble sleeping.

Eyes: Changes in vision as a result of cataracts; blurred vision; thinning of the surface of the eye; existing eye infections may get worse; glaucoma (increased pressure in the eye); bulging eyes.

Heart problems: Increased damage to the heart in the event of a heart attack; heart failure; high blood pressure; blood clots.

Stomach or digestive problems: Bleeding from your gut (which may result in stomach pain and/or blood in your stools which may look dark); an inflamed pancreas (which may result in nausea and vomiting with stomach and back pain); stomach pain and discomfort, bloated feeling; infection or ulceration of the gullet (the tube that connects your mouth with your stomach), which can cause chest pain, heartburn and/or difficulty or pain upon swallowing; indigestion; feeling sick.

Skin: Slow healing of cuts or wounds; thin or delicate skin; redness; stretch marks; bruising, red or purple spots, acne; sweating; wrong results from skin tests; growth of body hair.

Bone, muscle or joints: Muscle weakness or wasting; osteoporosis (thinner bones with a higher risk of breaking them, especially in older women); fractures of the vertebrae of the backbone, leg and arm bones; hip or shoulder pain due to problems with the blood supply to the bones; risk of torn tendons.

In men: Change in number and mobility of sperm.

In women: Irregular periods, facial hair.

Respiratory problems: Hiccups.

Investigations: Changes in the levels of various chemicals in the blood, which are usually detected by blood or urine tests; intolerance to carbohydrates; high blood glucose (which may be seen as excessive thirst and passing excessive amounts of urine).

Your doctor will want to see you now and then to look out for these effects. If you notice any of these, or if you get any other unusual feelings or symptoms, keep taking the tablets but contact your doctor or pharmacist as soon as you can. See also **Section 3, Before you take Hydrocortisone Tablets**, above.

IMPORTANT!

Do not reduce the dose of hydrocortisone too quickly (eg after illness), as your blood pressure could drop dangerously low. It may also cause 'withdrawal' symptoms (including pains in the muscles or joints, fever and general discomfort). Your doctor or pharmacist will give you advice on how to reduce the number of tablets you take if you need to do this.

6. Storing Hydrocortisone Tablets

Keep the tablets out of the reach and sight of children.

Keep the blister in the outer carton in order to protect from light.

You must not take Hydrocortisone Tablets after the date (month and year) printed after "EXP" on the blister and box. If the expiry date has passed, take the tablets back to your pharmacist.

If your doctor tells you to stop taking Hydrocortisone Tablets and you still have some tablets left, take them to your pharmacist.

7. What is in Hydrocortisone Tablets?

Hydrocortisone Tablets come in 2 strengths, 10 mg and 20 mg.

Active substance:
10 mg Tablets: Each tablet contains 10 mg hydrocortisone.
20 mg Tablets: Each tablet contains 20 mg hydrocortisone.

Other ingredients:
Maize starch, lactose, Povidone K90, magnesium stearate, talc and colloidal anhydrous silica.

Hydrocortisone 10 mg Tablets are round, white, with 'H 10' imprinted on one side and a breakline on the other;
Hydrocortisone 20 mg Tablets are round, white, with 'H 20' imprinted on one side and a breakline on the other.

Each box of Hydrocortisone Tablets contains 30 tablets, packed in blister strips.

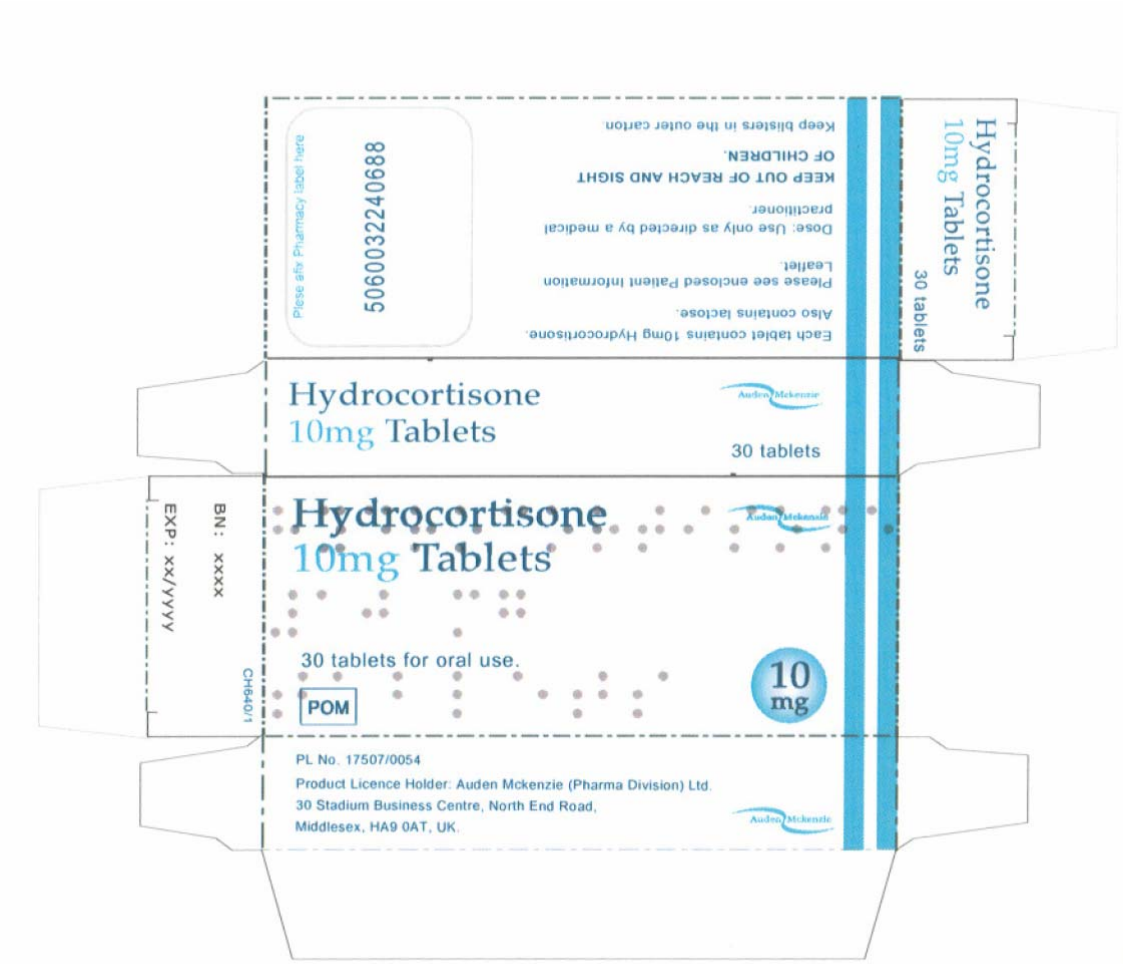
8. Addresses

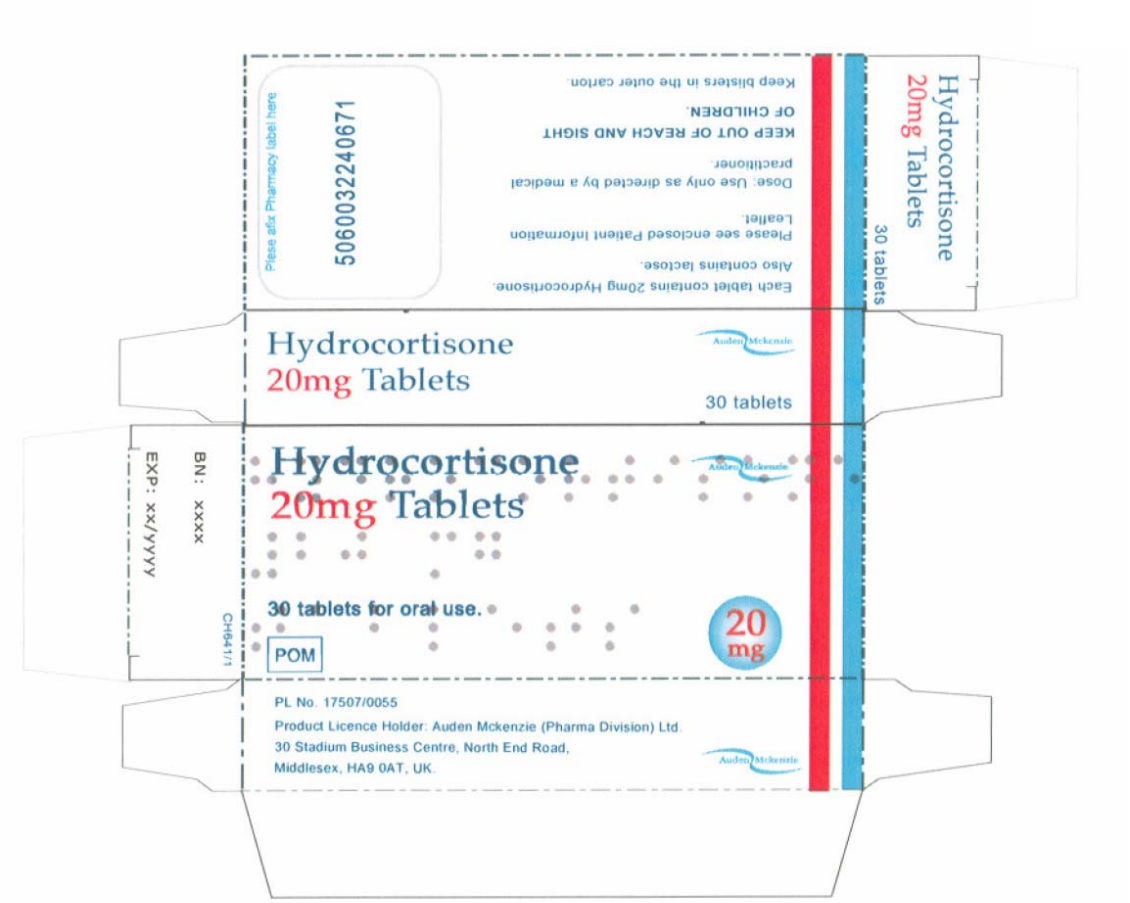
Marketing Authorisation holder
Auden Mckenzie (Pharma Division) Ltd
30 Stadium Business Centre
North End Road, Middlesex
HA9 0AT
UK

Manufacturer
TioFarma BV
Benjamin Franklinstraat 9, Oud-Beijerland
The Netherlands

Date of preparation of this leaflet: February 2007

LABELLING


Hydrocortisone
10mg Tablets
30 tablets
5060032240688
Please affix Pharmacy label here
Keep blisters in the outer carton
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
Dose: Use only as directed by a medical practitioner.
Please see enclosed Patient Information Leaflet.
Also contains lactose.
Each tablet contains 10mg Hydrocortisone.
Hydrocortisone
10mg Tablets
30 tablets
Hydrocortisone
10mg Tablets
30 tablets for oral use.
POM
10 mg
BN: xxxx
EXP: xx/yyyy
CH640/1
PL No. 17507/0054
Product Licence Holder: Auden Mckenzie (Pharma Division) Ltd.
30 Stadium Business Centre, North End Road,
Middlesex, HA9 0AT, UK.


Hydrocortisone
20mg Tablets
30 tablets
Hydrocortisone
20mg Tablets
30 tablets for oral use.
POM
20 mg
BN: xxxx
EXP: xx/yyyy
CH641/1
PL No. 17507/0055
Product Licence Holder: Auden Mckenzie (Pharma Division) Ltd.
30 Stadium Business Centre, North End Road,
Middlesex, HA9 0AT, UK.
5060032240671
Please affix Pharmacy label here
Each tablet contains 20mg Hydrocortisone.
Also contains lactose.
Please see enclosed Patient Information Leaflet.
Dose: Use only as directed by a medical practitioner.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.
Keep blisters in the outer carton.