1 NAME OF THE MEDICINAL PRODUCT

Fludrocortisone acetate 0.1 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains fludrocortisone acetate 0.1 mg

Also contains lactose, 59.59mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral tablet.

White, round, biconvex tablets, scored on one side and engraved on the other side with “FT01”. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For partial replacement therapy for primary adrenocortical insufficiency in Addison's disease and for the treatment of salt-losing adrenogenital syndrome.

4.2 Posology and method of administration

Adults:

A daily dosage range of 0.05-0.3mg Fludrocortisone acetate tablets orally. Supplementary parenteral administration of sodium-retaining hormones is not necessary. When an enhanced glucocorticoid effect is desirable, cortisone or hydrocortisone by mouth should be given concomitantly with Fludrocortisone acetate tablets.

Elderly:

No specific dosage recommendations (See Section 4.4).

Paediatric population:

One half tablet (0.05 mg) to one tablet (0.1 mg) daily. Caution should be used in the event of exposure to chickenpox, measles or other communicable diseases (See Section 4.3).

4.3 Contraindications

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

Systemic infections unless specific anti-infective therapy is employed.

Because of its marked effect on sodium retention, the use of Fludrocortisone acetate in the treatment of conditions other than those indicated, is not advised.

Since Fludrocortisone acetate is a potent mineralocorticoid both the dosage and salt intake should be carefully monitored to avoid the development of hypertension, oedema or weight gain. Periodic checking of serum electrolyte levels is advisable during prolonged therapy.

4.4 Special warnings and precautions for use

Fludrocortisone acetate is a potent mineralocorticoid and is used predominantly for replacement therapy. Although glucocorticoid side effects may occur, these can be reduced by reducing the dosage.

Undesirable effects may be minimised using the lowest effective dose for the minimum period. Frequent patient review is required to titrate the dose appropriately against disease activity (See Section 4.2).

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 and should be tapered off over weeks or months according to the dose and duration of treatment. Patients on long-term systemic therapy with Fludrocortisone acetate may require supportive corticosteroid therapy in times of stress (such as trauma, surgery or severe illness) both during the treatment period and up to a year afterwards. If corticosteroids have been stopped following prolonged therapy they may need to be reintroduced temporarily.

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

Anti-inflammatory/immunosuppressive effects:
Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

Chickenpox, shingles and measles are of particular concern since these illnesses may be fatal in immunosuppressed patients. Patients should be advised to avoid exposure to these diseases, and to seek medical advice without delay if exposure occurs.

Chickenpox: Unless they have had chickenpox, patients receiving oral corticosteroids for purposes other than replacement should be regarded as being *at risk of severe chickenpox*. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. 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 preferably be given within 3 days of exposure, and not later than 10 days after exposure to chickenpox. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Measles: Prophylaxis with normal immunoglobulin may be needed.
During corticosteroid therapy antibody response will be reduced and therefore affect the patient's response to vaccines. Live vaccines should not be administered.

Corticosteroids may affect the nitroblue tetrazolium test for bacterial infection, producing false negative results.

Tuberculosis: Those with a previous history of, or X-ray changes characteristic of, tuberculosis. The emergence of active tuberculosis can, however, be prevented by the prophylactic use of anti-tuberculosis therapy.

Chemoprophylaxis should be used in patients with latent tuberculosis or tuberculin reactivity who are taking corticosteroids.

Corticosteroids should be used with caution in patients with the following conditions: nonspecific ulcerative colitis (if there is a probability of perforation, abscess, or other pyogenic infection); recent intestinal anastomoses; diverticulitis; thrombophlebitis; existing or previous history of severe affective disorders (especially previous steroid psychosis); exanthematous disease; chronic nephritis or renal insufficiency; metastatic carcinoma; osteoporosis (post-menopausal females are particularly at risk); in patients with an active or latent peptic ulcer (or a history of peptic ulcer); myasthenia gravis; latent or healed tuberculosis, in the presence of local or systemic viral infection, systemic fungal infections or in active infections not controlled by antibiotics; in acute psychoses, in acute glomerulonephritis; hypertension, congestive heart failure; glaucoma (or a family history of glaucoma), previous steroid myopathy or epilepsy. Liver failure.

Pheochromocytoma crisis

Several life-threatening and fatal cases of pheochromocytoma crisis has been reported following administration of systemic corticosteroids to patients with suspected or identified pheochromocytoma. Use of corticosteroids in these patients should only be considered after an appropriate risk/benefit evaluation.

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.

Corticosteroid effects may be enhanced in patients with hypothyroidism or decreased in hyperthyroid patients.

Corticosteroid effects may be enhanced in patients with cirrhosis.

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

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

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.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts or glaucoma, with possible damage to the optic nerve. Prolonged use may also enhance the likelihood of secondary ocular infections.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.
All corticosteroids increase calcium excretion, which may predispose to osteoporosis or aggravate pre-existing osteoporosis.

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 pharmacokinetic interactions that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, 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.

Pre-existing emotional instability or psychosis may also be aggravated by corticosteroids. Fludrocortisone should be used with caution in patients with, or with a previous history of, severe affective disorders. Fludrocortisone should also be used with caution in patients who have a first degree relative(s) with any existing, or previous history of, severe affective disorders. Specifically, these include depressive or maniac-depressive illness and previous steroid psychosis. The use of antidepressant drugs does not relieve and may exacerbate adrenocorticoid-induced mental disturbances.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or 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.

Paediatric population:
Because corticosteroids can suppress growth, the growth and development of infants, children and adolescents on prolonged corticosteroid therapy should be carefully monitored. Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence which may be irreversible.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Amphotericin B injection and potassium-depleting agents: Patients should be observed for hypokalemia.

Anticholinesterases: Effects of anticholinesterase agents may be antagonised.

Anticoagulants, oral: Corticosteroids may potentiate or decrease anticoagulant action. Patients receiving oral anticoagulants and corticosteroids should therefore be closely monitored.

Antidiabetics: Corticosteroids may increase blood glucose; diabetic control should be monitored, especially when corticosteroids are initiated, discontinued, or changed in dosage.

Antihypertensives, including diuretics: corticosteroids antagonise the effects of antihypertensives and diuretics. The hypokalaemic effect of diuretics, including acetazolamide, is enhanced.

Anti-tubercular drugs: Isoniazid serum concentrations may be decreased.

Cyclosporin: Monitor for evidence of increased toxicity of cyclosporin when the two are used concurrently.

CYP3A inhibitors: 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.

Digitalis glycosides: Enhanced possibility of arrhythmias or digitalis toxicity associated with hypokalemia.

Oestrogens, including oral contraceptives: Corticosteroid half-life and concentration may be increased and clearance decreased. A reduction in corticosteroid dosage may be required when oestrogen therapy is initiated, and an increase required when oestrogen is stopped.

Hepatic Enzyme Inducers (e.g. aminoglutethemide, barbiturates, carbamazepine, phenytoin, primidone, rifabutin, rifampicin): There may be increased metabolic clearance of Fludrocortisone acetate. Patients should be carefully observed for possible diminished effect of steroid, and the dosage should be adjusted accordingly.

Human growth hormone: The growth-promoting effect may be inhibited.

Ketoconazole: Corticosteroid clearance may be decreased, resulting in increased effects.

Nondepolarising muscle relaxants: Corticosteroids may decrease or enhance the neuromuscular blocking action.

Nonsteroidal anti-inflammatory agents (NSAIDS): Corticosteroids may increase the incidence and/or severity of GI bleeding and ulceration associated with NSAIDS. Also, corticosteroids can reduce serum salicylate levels and therefore decrease their effectiveness. Conversely, discontinuing corticosteroids during high-dose salicylate therapy may result in salicylate toxicity. Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypoprothrombinaemia.

Thyroid drugs: Metabolic clearance of adrenocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in adrenocorticoid dosage.

Vaccines: Neurological complications and lack of antibody response may occur when patients taking corticosteroids are vaccinated (See Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
It may be decided to continue a pregnancy in a woman requiring replacement mineralocorticoid therapy, despite the risk to the foetus. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

There is evidence of harmful effects in pregnancy in animals. There may be a small risk of cleft palate and intra-uterine growth retardation. Hypoadrenalism may occur in the neonate. Patients with pre-eclampsia or fluid retention require close monitoring.

Breast-feeding
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

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

Most adverse reactions to fludrocortisone acetate are caused by the drug’s mineralocorticoid activity and include hypertension, oedema, cardiac enlargement, congestive heart failure, potassium loss, and hypokalemic alkalosis.

Where adverse reactions occur they are usually reversible on cessation of therapy. The incidence of predictable side-effects, including hypothalamic-pituitary-adrenal suppression correlate with the relative potency of the drug, dosage, timing of administration and duration of treatment (See Section 4.4).

Tabulated list of adverse reactions

The list below is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories:

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)

System Organ Class	Frequency	MedDRA Terms
Metabolism and nutrition disorders	Very common	Hypokalaemia
	Uncommon	Hypokalaemic alkolosis ; Decreased appetite
Psychiatric disorders	Uncommon	Delusional perception, illusion
	Uncommon	hallucination
Nervous System disorders	Common	Headache
	Uncommon	seizure, epilepsy, syncope, loss of consciousness, dysgeusia
Cardiac disorders	Very common	cardiac failure congestive
	Uncommon	Cardiomegaly
Vascular disorders	Very common	Hypertension
Gastrointestinal disorders	Uncommon	Diarrhoea
Musculoskeletal and connective tissue disorders	Common	Muscular weakness
	Uncommon	Muscle atrophy

General disorders and administration site conditions	Common	Oedema, swelling
Investigations	Uncommon	blood potassium decreased

Description of selected adverse reactions

When fludrocortisone is used at the recommended dosages, the glucocorticoid side effects are not usually present; however, the following adverse events have been spontaneously reported in two or more patients taking Fludrocortisone acetate overdose.

Withdrawal Symptoms and Signs:

On withdrawal, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss may occur. Too rapid a reduction in dose following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (See Section 4.4).

Patients should be watched closely for the following adverse reactions which may be associated with any corticosteroid therapy:

Anti-inflammatory and immunosuppressive effects: Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (See Section 4.4).

Fluid and electrolyte disturbances: sodium retention, fluid retention, , cardiac arrhythmias or ECG changes due to potassium deficiency and increased calcium excretion.

Musculoskeletal and connective tissue disorders:fatigue, steroid myopathy, loss of muscle mass, osteoporosis, avascular osteonecrosis, vertebral compression fractures, delayed healing of fractures, aseptic necrosis of femoral and humeral heads, pathological fractures of long bones and spontaneous fractures, tendon rupture.

Gastrointestinal disorders: dyspepsia, peptic ulcer with possible subsequent perforation and haemorrhage, pancreatitis, abdominal distension and ulcerative oesophagitis, candidiasis.

Hypersensitivity: Anaphylatic reactions, angioedema, rash, pruritus and urticaria, particularly where there is a history of drug allergies.

Skin and subcutaneous tissue disorders: impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, purpura, striae, hirsutism, acneiform eruptions, lupus erythematosus-like lesions and suppressed reactions to skin tests.

Nervous system disorders: euphoria, psychological dependence, depression, insomnia, increased intracranial pressure with papilloedema (pseudo-tumour cerebri) usually after treatment, vertigo, neuritis or paraesthesias and aggravation of pre-existing psychiatric conditions.

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

Endocrine disorders/metabolic and nutrition disorders: menstrual irregularities and amenorrhoea; development of the Cushingoid state; suppression of growth in childhood and adolescence; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress (e.g. trauma, surgery or illness); decreased carbohydrate tolerance; manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycaemic agents in diabetes, weight gain. Negative protein and calcium balance. Increased appetite.

Eye disorders: posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases, vision, blurred (see also section 4.4).

Others: necrotising angiitis, thrombophlebitis, thromboembolism, leukocytosis, insomnia and syncopal episodes.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google Play or Apple App Store.

4.9 Overdose

Symptoms

Development of hypertension, oedema, hypokalaemia, significant increase in weight, and increase in heart size may be signs of excessive dosage of fludrocortisone acetate. Muscle weakness due to excessive potassium loss may develop and can be treated with potassium supplements.

Management

When symptoms of excessive dosage of fludrocortisone acetate (listed above) are noted, administration of the drug should be discontinued, after which the symptoms will usually subside within several days; subsequent treatment with fludrocortisone acetate, if necessary, should be resumed at a reduced dose.

For large, acute overdoses, treatment includes gastric lavage or emesis and usual supportive measures. A single large dose should be treated with plenty of water by mouth. Careful monitoring of serum electrolytes is essential, with particular consideration being given to the need for administration of potassium chloride and restriction of dietary sodium intake.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mineralocorticoids, ATC code: H02AA02

Qualitatively, the physiological action of fludrocortisone acetate is similar to hydrocortisone. In very small doses, fludrocortisone maintains life in adrenalectomised animals, enhances the deposition of liver glycogen and produces thymic involution, eosinopenia, retention of sodium and increased urinary excretion of potassium.

5.2 Pharmacokinetic properties

Fludrocortisone is rapidly and completely absorbed after oral administration. Man, dog, rat, monkey and guinea-pig were studied after i.v. and intraduodenal administration. Depending on species, 50% or more of the steroid remained unchanged 30 minutes after administration. Fludrocortisone is hydrolysed to produce the non-esterified alcohol; after administration of the acetate, only the non-esterified alcohol is detectable in blood. The blood level reaches a peak between 4 and 8 hours. The highest blood level after i.v. administration to human volunteers was 1.7 hours.

Elimination half-life after i.v. administration was 30 minutes in dogs and in human volunteers. Following administration of the acetate to dogs, the blood concentration shows a triphasic decline and each phase may represent the elimination of a metabolite.

Fludrocortisone is widely distributed throughout the body. It is 70 to 80% bound to serum proteins, mainly to the globulin fractions. The concentrations ratio of the drug in CSF to that in plasma was 1:6 in human volunteers.

In rats, most of a dose is excreted in the bile, and in dogs and guinea-pigs most of the dose is excreted in the urine. In human volunteers, excretion through urine was about 80%, and it was concluded that about 20% were excreted by a different route. It is likely that, as for the metabolism of other steroids, excretion into the bile is balanced by re-absorption in the intestine and some part is excreted with the faeces.

5.3 Preclinical safety data

No studies have been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, dibasic calcium phosphate, lactose anhydrous and monohydrate, talc, sodium benzoate (E211), magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Keep the bottle tightly closed to protect from moisture. Excursions to room temperature (25°C) are permitted for up to 30 days. After temperature excursion, do not return unused tablets to refrigerated storage and dispose of such tablets.

6.5 Nature and contents of container

Amber glass bottles of 100 tablets with a cotton plug, induction seal and polypropylene caps.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited,

3016 Lake Drive,

Citywest Business Campus,

Dublin 24,

Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 39699/0071

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/03/2011

10 DATE OF REVISION OF THE TEXT

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