Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fludrocortisone acetate 0.1 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains fludrocortisone acetate 0.1mg.

Excipient with known effect:
Also contains lactose, 59.59mg per tablet and sodium benzoate, 0.010mg per tablet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, round, biconvex tablets, scored on one side and engraved on the other side with "FT01". The tablets 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

Addison's Disease

A daily dosage range of 0.05 to 0.3mg Fludrocortisone acetate tablets orally. Supplementary parenteral administration of sodium-retaining hormones is not necessary. When an enhanced glucocorticoid effect is necessary, this should be achieved by concurrent administration of cortisone (6.25 to 25mg) or hydrocortisone (5 to 20mg) daily.

Salt-losing Adrenogenital Syndrome

The recommended oral dosage for treating salt-losing adrenogenital syndrome is one tablet (0.1mg) to two tablets (0. 2mg) of Fludrocortisone acetate daily. Restriction of sodium intake and supplementary potassium administration may be required.

Paediatric population

One half tablet (0.05 mg) to one tablet (0.1 mg) daily. Daily dosage should be adjusted to the age and weight of the child and the severity of the condition. Caution should be used in the event of exposure to chickenpox, measles or other communicable diseases. (See section 4.4).

Elderly

No specific dosing recommendations (see section 4.4).

4.3 Contraindications

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

Use in patients with peptic ulcer, active tuberculosis, acute psychosis, acute bacterial or viral infection.

Use in patients hypersensitive to the product components.

Systemic infections unless specific anti-infective therapy is employed.

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

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.

Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion, which may predispose to osteoporosis or aggravate pre-existing osteoporosis

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 normally minor 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.

Fludrocortisone acetate is contraindicated for use in active tuberculosis (see section 4.3). Chemoprophylaxis should be used in patients with latent tuberculosis or tuberculin reactivity who are taking corticosteroids.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation

of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Corticosteroids should be used 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; recent intestinal anastomoses; thrombophlebitis; existing or previous history of severe affective disorders (especially previous steroid psychosis);exanthematous disease; chronic nephritisor 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.

An adequate protein intake is advised for patients on long-term corticosteroids to counteract any tendency to weight-loss or muscle wasting/weakness associated with negative nitrogen balance.

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

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

This medicine contains lactose., patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains 0.010 mg of benzoate salt in each tablet.
Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

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.

There have been a few reports in the literature of the development of cataracts in patients who have been using corticosteroids for prolonged periods of time. Although it is not possible to rule out systemic corticosteroids as a known factor, prescribers should be aware of the possible role of corticosteroids in cataract development.

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

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.
Preexisting emotional instability or psychosis may also be aggravated by corticosteroids. 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
Growth and development of children on prolonged corticosteroid therapy should be carefully observed. Prolonged use in children may lead to growth retardation. Some recovery may occur on discontinuing the drug.

Corticosteroids may also affect endogenous steroid production

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 hypokalaemia. Potassium levels should be checked at frequent intervals and potassium supplements used if necessary.

Anti-cholinesterases: Effects of anticholinesterase agents may be antagonised.

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

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

Anti-hypertensives, 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. Potassium levels should be monitored and potassium supplements used if necessary**.**

Oestrogens, include 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.

Non-depolarising muscle relaxants: Corticosteroids may decrease or enhance the neuromuscular blocking action.

Non-steroidal 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

Fludrocortisone acetate can be used as replacement therapy during pregnancy. There are no indications that replacement therapy with fludrocortisone in pregnant women is associated with adverse consequences for the foetus.
Corticosteroids have been shown to be teratogenic in some animal species. Animal studies are insufficient with respect to reproductive toxicity of fludrocortisone (see section 5.3).

Infants born of mothers who have received substantial doses of fludrocortisone acetate during pregnancy should be carefully observed for signs of adrenal suppression.

Breastfeeding

It is not known whether fludrocortisone acetate is excreted in human milk. Other systemic corticosteroids have been shown to appear in breast milk.

Breastfeeding may be maintained during replacement therapy with Fludrocortisone acetate at the recommended low doses.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Corticosteroid administration will result in certain effects, the severity, significance and extent of which vary with the dosage and duration of treatment and the particular corticosteroid used.

These include disturbance in electrolyte balance, mineral metabolism, glucose metabolism and gluconeogenesis, nitrogen depletion, diminished lymphoid tissue and immune response, inhibition of pituitary function, Cushingoid Syndrome, increase in blood coagulability, diminished inflammatory response. Cataracts, psychosis, mood changes, avascular osteo necrosis and pancreatitis may occur. Other areas affected include musculoskeletal, gastrointestinal, dermatologic, neurological and endocrine.

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.

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.

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: anorexia convulsions, diarrhoea, headache, muscle atrophy, myasthenia, overdose, syncope, taste perversion, hallucinations.

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, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000) and very rare (< 1/10,000), and not known (cannot be estimated from the available data)

System Organ Class	**Frequency**	**MedDRA Terms**
Metabolism and nutrition disorders	Uncommon	Hypokalaemic alkalosis, Decreased appetite
Nervous System disorders	Common	Headache
	Uncommon	Convulsion, seizure, epilepsy, syncope, loss of consciousness, dysgeusia, hallucination, perception disturbance
Cardiac disorders	Very common	Congestive Heart Failure
	Uncommon	Cardiacmegaly
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	Edema, swelling
Investigations	Very common	Hypokalaemia
	Uncommon	K+ decrease
Injury, poisoning and procedural complications	Uncommon	Overdose
Eye disorder	Not known	Vision, blurred (see also section 4.4)

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 HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

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

Acute
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

Corticosteroids are thought to act, at least in part, by controlling the rate of synthesis of proteins at the cellular level. The relationship between this activity and the metabolic effects is not yet totally clear.

The physiologic action of fludrocortisone acetate is similar to that of hydrocortisone but the glucocorticoid effect is 15 times as potent and the mineralocorticoid effect is 125 times greater. Sodium reabsorption in the renal distal tubules and in other tissues appears to account for the physiologic action characteristic of mineralocorticoids. Small doses of these drugs result in marked sodium retention and increased urinary excretion of potassium and hydrogen.

Blood pressure is also elevated apparently because of these effects on electrolytes. Larger doses inhibit endogenous adrenal cortical secretion, thymic activity, and pituitary corticotropin excretion; high doses also promote the deposition of liver glycogen, and unless protein intake is adequate, induce negative nitrogen balance.

5.2 Pharmacokinetic properties

Absorption
A potent mineralocorticoid with some glucocorticoid properties, well absorbed, metabolised slowly with a T½ of up to 30 hours. It has strong sodium retaining capacity.

Elimination
Fludrocortisone is highly protein bound and is eliminated by the kidneys, mostly as inactive metabolites. The pharmacodynamic half-life of fludrocortisone is approximately 18 to 36 hours. The duration of action is 1 to 2 days.

5.3 Preclinical safety data

There are not sufficient data to determine whether fludrocortisone acetate is carcinogenic, mutagenic, or impairs fertility in males or females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic calcium phosphate
Lactose anhydrous
Lactose monohydrate
Talc
Maize starch
Magnesium stearate
Sodium benzoate (E211)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Between 2^{o}C and 8^{o}C: 24 months
Excursion from 2^{o}C-8^{o}C to 25^{o}C: up to 1 month

6.4 Special precautions for storage

Store in a refrigerator (2^{o}C-8°C). Keep the bottle tightly closed to protect from moisture. Excursions to 25^{o}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

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

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA2010/064/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1st April 2008

10 DATE OF REVISION OF THE TEXT

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