FLORINEF TABLET 0.1 mg
FLUDROCORTISONE ACETATE

DESCRIPTION
Round, uniform, biconvex, white practically odourless tablets. They are free from visible impurities. They are scored on one side and engraved on other side with **"FT01".**

FLORINEF tablet : Each tablet contains 0.1mg of fludrocortisone acetate and the following inactive ingredients : cornstarch, dicalcium phosphate, lactose, magnesium stearate, sodium benzoate and talc.

PHARMACOLOGY
The active ingredient in **FLORINEF** tablets is fludrocortisone (also known as fluo(ro)hydrocortisone or fluohydrisone) acetate, a synthetic adrenocortical steroid with potent mineralocorticoid properties and high glucocorticoid activity. It is used for its mineralocorticoid effects.

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.

The approximate half-life of fludrocortisone is 18 to 36 hours. It is highly protein bound and is eliminated by the kidneys, mostly as inactive metabolites. Duration of action is 1 to 2 days.

INDICATIONS AND USAGE
FLORINEF is indicated as partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease and for the treatment of salt-losing adrenogenital syndrome.

CONTRAINDICATIONS
Corticosteroids are contraindicated in patients with systemic fungal infections and in those with suspected or known hypersensitivity to fludrocortisone or any of the inactive ingredients.

WARNINGS AND PRECAUTIONS FOR USE
Moderate and high doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Since fludrocortisone is a potent mineralocorticoid, both dosage and salt intake should be carefully monitored to avoid hypertension, edema, or weight gain.

FLORINEF should not be used in patients with uncontrolled congestive heart failure. Electrolyte levels should be checked during prolonged therapy. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion, which may predispose to osteoporosis or aggravate preexisting osteoporosis.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Chicken pox, measles, herpes zoster, or threadworm infestations, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

Patients should not be vaccinated or immunized while on corticosteroid therapy, especially on high doses, because of a lack of antibody response predisposing to medical complications, particularly neurological ones.

The use of fludrocortisone acetate tablets in patients with active tuberculosis should be restricted to cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen. Chemoprophylaxis should be used in patients with latent tuberculosis or tuberculin reactivity who are taking corticosteroids.

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.

Adverse reactions to corticosteroids may be produced by too rapid withdrawal or by continued use of large doses.

To avoid drug-induced adrenal insufficiency, supportive dosage may be required in times of stress (such as trauma, surgery, or severe illness) both during treatment with **FLORINEF** and for a year afterwards.

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

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Psychiatric disturbances may appear with corticosteroid use. These can include insomnia, depression (sometimes severe), euphoria, mood swings, psychotic symptoms and personality changes. 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.

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); diverticulitis; recent intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; acuteglomerulonephritis; chronic nephritis; hypertension; congestive heart failure; thrombophlebitis; thromboembolism; osteoporosis; exanthema; Cushing's syndrome; diabetes mellitus; convulsive disorders; metastatic carcinoma; and myasthenia gravis. Further, corticosteroid therapy has caused menstrual irregularities and hyperacidity or peptic ulcer. 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.

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.

INFORMATION FOR PATIENTS
The physician should advise the patient to report any medical history of heart disease, high blood pressure, or kidney or liver disease and to report current use of any medicines to determine whether these medicines might interact adversely with fludrocortisone (see also INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

The patient should be informed of his steroid-dependent status, which should be monitored periodically by a physician. Increased dosage is required under widely variable conditions of stress (e.g., trauma, surgery, severe illness).

The patient should be advised to promptly notify the physician of dizziness, severe or continuing headaches, swelling of feet or legs, or unusual weight gain.

The patient should be instructed to take a missed dose as soon as possible, unless it is almost time for the next dose, and not to double the next dose. The patient also should be warned against abruptly withdrawing from corticosteroid therapy.

LABORATORY TESTS
Patients should be monitored regularly for blood pressure and serum electrolyte determinations (see WARNINGS AND PRECAUTIONS FOR USE).

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
When administered concurrently, the following drugs may interact with adrenal corticosteroids:

Amphotericin B or potassium - depleting diuretics

(benzothiadiazines and related drugs, ethacrynic acid and furosemide) - Enhanced hypokalemia. Potassium levels should be checked at frequent intervals and potassium supplements used if necessary (see WARNINGS AND PRECAUTIONS FOR USE).

Anticholinesterases - Effects of the anticholinesterase agent may be antagonized.

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

Antidiabetics (oral agents and insulin) - Diminished antidiabetic effect. Patient should be monitored for symptoms of hyperglycemia; dosage of antidiabetic drug should be adjusted if necessary.

Antitubercular drugs - Isoniazid serum concentrations may be decreased in some patients.

Cyclosporine - Increased activity of both cyclosporine and corticosteroids may occur 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

PHARMA CODE N° xxxx

if necessary.

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

Hepatic enzyme inducers (e.g., barbiturates, phenytoin,carbamazepine, rifampin) - Increased metabolic clearance of fludrocortisone. Patients should be observed for possible diminished effect of steroid, and the dosage of **FLORINEF** should be adjusted accordingly.

Human growth hormone - The growth-promoting effect of human growth hormone may be inhibited.

Ketoconazole - Corticosteroid clearance may be decreased, resulting in increased therapeutic effect.

Nondepolarizing muscle relaxants - Corticosteroids may decrease or enhance the neuromuscular blocking action.

Nonsteroidal anti-inflammatory agents (NSAIDs) - Increased ulcerogenic effect; decreased pharmacologic effect of aspirin. Conversely, salicylate toxicity may occur in patients who discontinue steroids with concurrent high-dose aspirin therapy. Corticosteroids should be used cautiously in conjunction with aspirin in patients with hypoprothrombinemia.

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 WARNINGS AND PRECAUTIONS FOR USE).

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

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

PREGNANCY AND LACTATION
Many corticosteroids have been shown to be teratogenic in laboratory animals at low doses. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of child bearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and the embryo, fetus, or breast-fed infant. Other systemic corticosteroids have been shown to appear in breast milk and to slightly elevate (by 1%) the risk of cleft palate in human fetuses. Infants born to mothers who have received substantial doses of fludrocortisone acetate during pregnancy should be carefully observed for signs of adrenal suppression.

PEDIATRIC USE
Because corticosteroids can suppress growth, the growth and development of infants, children, and adolescents on prolonged corticosteroid therapy should be carefully monitored. Caution should be used in the event of chicken pox, measles, or other communicable diseases. Children should not be vaccinated while on therapy with **FLORINEF** (see WARNINGS AND PRECAUTIONS FOR USE). Corticosteroids may also affect endogenous steroid production.

GERIATRIC USE
The adverse effects of systemic corticosteroids, such as osteoporosis or hypertension, may be associated with more serious consequences in the elderly. Close clinical supervision is therefore recommended.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
The effects of corticosteroid therapy on the ability to drive or operate machinery have not been studied.

UNDESIRABLE EFFECTS
Most adverse reactions to **FLORINEF** are caused by the drug's mineralocorticoid activity and include hypertension, edema, cardiac enlargement, congestive heart failure, potassium loss, and hypokalemic alkalosis.

When fludrocortisone is used in the small dosages recommended, the glucocorticoid side effects often seen with cortisone and its derivatives are not usually a problem. However, the following adverse events have been spontaneously reported in two or more patients taking **FLORINEF**: anorexia, convulsions, diarrhea, headache, muscle atrophy, myasthenia, overdose, syncope, taste perversion, hallucinations. The following untoward effects should be kept in mind, particularly when fludrocortisone is used over a prolonged period of time or in conjunction with cortisone or a similar glucocorticoid.

Musculoskeletal : Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, and spontaneous fractures.

Gastrointestinal : Peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distension, and ulcerative esophagitis.

Dermatologic : Impaired wound healing, thin fragile skin, bruising, petechiae and ecchymoses, facial erythema, increased sweating, subcutaneous fat atrophy, purpura, striae, hyperpigmentation of the skin and nails, hirsutism, acneiform eruptions, and hives and/or allergic skin rash; reactions to skin tests may be suppressed.

Neurological : Convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache, and severe mental disturbances.

Endocrine : Menstrual irregularities; development of the cushingoid state; supression of growth in children; 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 hypoglycemic agents in diabetics.

Ophthalmic : Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and exophthalmos.

Frequency not known (cannot be estimated from available data): Blurred vision*

* see section WARNINGS AND PRECAUTION FOR USE

Contact your doctor if you experience blurred vision or other visual disturbances.

Metabolic : Hyperglycemia, glycosuria, and negative nitrogen balance due to protein catabolism.

Other adverse reactions that may occur following the administration of a corticosteroid are necrotizing angitis, thrombophlebitis, aggravation or masking infections, insomnia, syncopal episodes, and anaphylactoid reactions.

OVERDOSAGE
Chronic : Development of hypertension, edema, hypokalemia, significant increase in weight, and increase in heart size may be signs of excessive dosage of **FLORINEF**. When these are noted, administration of the drug should be discontinued, after which the symptoms will usually subside within several days; subsequent treatment with **FLORINEF**, 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. Monitoring of blood pressure and serum electrolytes can reduce the likelihood of consequences of excessive dosage (see WARNINGS AND PRECAUTIONS FOR USE).

Acute : For large, acute overdoses, treatment includes gastric lavage or emesis and usual supportive measures.

RECOMMENDED DOSAGE
Dosage depends on the severity of the disease and the response of the patient. The lowest possible dose should be used to control the condition being treated, and a reduction in dosage should be made (gradually) when possible.

Adrenocorticoid Insufficiency (chronic).
In Addison's disease, the combination of **FLORINEF** with a glucocorticoid such as hydrocortisone or cortisone provides substitution therapy approximating normal adrenal activity.

The usual dose for adults, adolescents, and elderly patients is one tablet (0.1 mg) of **FLORINEF** daily - range: one tablet (0.1 mg) three times a week to two tablets (0.2 mg) daily. If treatment-associated hypertension develops, the dose should be reduced to 0.05 mg daily. **FLORINEF** is preferably administered in conjunction with cortisone (10 mg to 37.5 mg daily in divided doses) or hydrocortisone (10 mg to 30 mg daily in divided doses).

Salt-losing Adrenogenital Syndrome
The recommended dosage for treating salt-losing adrenogenital syndrome is one tablet (0.1 mg) to two tablets (0.2 mg) of **FLORINEF** daily.

Pediatric and Adolescent: One half tablet (0.05 mg) to one tablet (0.1 mg) daily.

STORAGE
Store refrigerated (2-8°C) in a well-closed container; avoid excessive heat.

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 properly.

Keep out of reach of children.

HOW SUPPLIED: Bottles of 100's individually cartoned, each accompanied with a package insert.

SHELF LIFE: 24 months

Product Owner:

Aspen Global Inc. Mauritius

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PHARMA CODE N° xxxx