

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Florinef tablet 0.1 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Florinef tablets contain 0.1 mg of fludrocortisone acetate as the active ingredient.

Fludrocortisone acetate is a white to pale yellow, odourless or almost odourless, crystalline powder. Practically insoluble in water; soluble 1 in 50 in alcohol, 1 in 50 in chloroform; slightly soluble in ether.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Florinef is a white, uncoated tablet with a score line on one side and "FT 01" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Addison's disease

The combination of Florinef with a glucocorticoid such as hydrocortisone or cortisone provides substitution therapy approximating normal adrenal activity with minimal risks of unwanted effects. The usual dose is 0.1 mg of Florinef daily, although dosage ranging from 0.1 mg three times a week to 0.2 mg daily has been employed. In the event transient hypertension develops as a consequence of therapy, the dose should be reduced to 0.05 mg daily. Florinef is preferably administered in conjunction with cortisone (10 to 37.5 mg daily in divided doses) or hydrocortisone (10 to 30 mg daily in divided doses).

Salt-losing adrenogenital syndrome

The recommended dosage is 0.1 to 0.2 mg of Florinef daily.

4.3 Contraindications

Patients with systemic fungal infections.

Patients with suspected or known hypersensitivity to fludrocortisone or any of the inactive ingredients.

Patients on high dose Florinef should not be administered live vaccines as the antibody response will be reduced (see section 4.4 Special warnings and precautions for use).

4.4 Special warnings and precautions for use

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

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids are used. If an infection occurs during fludrocortisone acetate therapy, it should be promptly controlled by suitable antimicrobial therapy. 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.

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.

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.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased potassium excretion. These effects are less likely to occur with the synthetic derivatives except when used in large doses. However, since fludrocortisone acetate is a potent mineralocorticoid, both the dosage and salt intake should be carefully monitored in order to avoid the development of hypertension, oedema or weight gain.

Florinef should not be used in patients with uncontrolled congestive heart failure.

Periodic checking of serum electrolyte levels is advisable 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.

Vaccination

Live vaccines are contraindicated in patients taking high doses of Florinef (see section 4.3 Contraindications). Live vaccines may, however, be administered to patients on maintenance therapy, although there may be a reduced response. Killed or inactivated vaccines do not represent a danger to immunocompromised patients and generally should be administered as for healthy children. However, there may be a reduced response.

The use of Florinef in patients with active tuberculosis should be restricted to those 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. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary since reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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 fludrocortisone acetate 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.

The lowest possible dose of corticosteroid should be used to control the condition being treated. A gradual reduction in dosage should be made when possible.

Psychiatric disturbances may appear when corticosteroids are used. These may range from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic tendencies may also be aggravated by corticosteroids.

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

The use of antidepressant drugs does not relieve and may exacerbate adreno-corticosteroid induced mental disturbances.

Corticosteroids should be used with caution in patients with nonspecific ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection.

Corticosteroids should also be used cautiously in patients with diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, acute glomerulonephritis, vaccinia, varicella, exanthema, Cushing's syndrome, antibiotic resistant infections, diabetes mellitus, congestive heart failure, chronic nephritis, thromboembolic tendencies, thrombophlebitis, convulsive disorders, metastatic carcinoma and

myasthenia gravis. Further, corticosteroid therapy has caused menstrual irregularities and hyperacidity or peptic ulcer.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

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

Patients should be monitored regularly for blood pressure and serum electrolyte levels.

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.

4.5 Interactions with other medicines 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 section 4.4 Special warnings and precautions for use).

Anticholinesterases

Effects of the anticholinesterase agent may be antagonized.

Anticoagulants oral

Corticosteroid 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.

Cyclosporin

Increased activity of both cyclosporin 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 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 (e.g. somatrem)

The growth-promoting effect of somatrem 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 section 4.4 Special warnings and precautions for use).

Laboratory test interactions

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

4.6 Fertility, pregnancy and lactation

Use in pregnancy (Category C)

In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations) and abortion. These findings do not seem to be relevant to humans. Reduced placental and birthweight have been recorded in animals and humans after long-term treatment. Since the possibility of suppression of the adrenal cortex in the newborn infant after long-term treatment must be considered, the needs of the mother must be carefully weighed against the risk to the foetus when prescribing these drugs. The short-term use of corticosteroids antepartum for the prevention of respiratory distress syndrome does not seem to pose a risk to the foetus or the newborn infant.

Infants born of mothers who have received substantial doses of fludrocortisone acetate during pregnancy should be carefully observed for signs of hypoadrenalism. Maternal pulmonary oedema has been reported with tocolysis and fluid overload.

Use in lactation

The use of this drug in nursing mothers requires that the possible benefits of the drug be weighed against the potential hazards to the child.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to <https://nzphvc.otago.ac.nz/reporting/>.

In the recommended small dosages, the side effects seen with cortisone and its derivatives are not usually a problem with fludrocortisone. However, the following untoward effects should be kept in mind, particularly when this agent is used over a prolonged period of time or in conjunction with cortisone or a similar glucocorticoid.

Fluid and electrolyte disturbances

Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalaemic alkalosis and hypertension.

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 haemorrhage, pancreatitis, abdominal distension, hyperacidity, ulcerative oesophagitis, anorexia, taste perversion and diarrhoea.

Dermatological

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, and acne-form eruptions; reactions to skin tests may be suppressed.

Neurological

Convulsions, increased intracranial pressure with papilloedema (pseudotumour cerebri) usually after treatment, vertigo, headache, severe mental disturbances and hallucinations.

Endocrine

Menstrual irregularities, development of the cushingoid state, suppression 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 hypoglycaemic agents in diabetes.

Ophthalmic

Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, central serous chorioretinopathy (CSCR) and exophthalmos.

Metabolic

Hyperglycaemia, glycosuria and negative nitrogen balance due to protein catabolism.

Other

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

Pediatric use

Safety and effectiveness of Florinef have not been established in children. Because corticosteroids can suppress growth, the growth and development of infants and 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 may be vaccinated while on maintenance therapy with Florinef (see section 4.4 Special 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.

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Chronic

Development of hypertension, oedema, 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 section 4.4 Special warnings and precautions for use).

Acute

For large, acute overdoses, treat symptomatically and institute usual supportive measures as required.

5. PHARMACOLOGICAL PROPERTIES

Fludrocortisone acetate is a synthetic adrenocortical steroid possessing very potent mineralcorticoid properties and high glucocorticoid activity. It is used for its mineralcorticoid effects.

5.1 Pharmacodynamic properties

Drug class: corticosteroid; glucocorticoid; ATC code: H02AA02

Actions

The physiological action is similar to that of hydrocortisone. However, the effects of fludrocortisone acetate, particularly on electrolyte balance, but also on carbohydrate metabolism, are considerably heightened and prolonged. In small oral doses, it produces marked sodium retention and increased urinary potassium excretion. It also causes a rise in blood pressure, apparently because of these effects on electrolyte levels.

5.2 Pharmacokinetic properties

In larger doses, fludrocortisone acetate inhibits endogenous adrenal cortical secretion, thymic activity, and pituitary corticotropin excretion; promotes the deposition of liver glycogen; and, unless protein intake is adequate, induced negative nitrogen balance. The approximate half-life of fludrocortisone is 18-36 hours. It is highly protein bound and is eliminated by the kidneys, mostly as inactive metabolites. Duration of action is 1 to 2 days.

5.3 Preclinical safety data

No data included.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, lactose anhydrous, calcium hydrogen phosphate dihydrate, maize starch, purified talc, magnesium stearate and sodium benzoate.

6.2 Incompatibilities

None reported.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at 2-8°C in a well closed container. Refrigerate, do not freeze.

Storage instruction at time of dispensing

On dispensing, the product can also be stored within the bottle below 25°C for a maximum of 3 months. The Start Date (Below 25°C) and Expiry Date (Below 25°C) sections on the Product Label must be filled-in at the time of dispensing as a record for the consumer. After this time discard all tablets that have not been refrigerated.

6.5 Nature and contents of container

Florinef tablets are supplied in a glass bottle. Each bottle contains 30 or 100 tablets.

Note: Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pharmacy Retailing (NZ) Limited trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland, New Zealand

Telephone: (09) 918 5100
Email: aspen@aspenpharma.co.nz

9. DATE OF FIRST APPROVAL

31/12/1969

10. DATE OF REVISION OF THE TEXT

10 December 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.4	Addition of storage information to align with labelling.
8	Addition of telephone and email.
all	Update to the SPC-style.
4.4, 4.5 & 4.8	4.4: Addition of 'visual disturbance' safety text at the request of Medsafe. 4.5: Addition of CYP3A inhibitors interaction due to the CCDS v06. 4.8: Addition of central serous chorioretinopathy (CSCR) as an adverse event at the request of Medsafe.
3	Change to tablet debossing.