PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr**FLORINEF®**

Fludrocortisone acetate tablets
Tablets, 0.1 mg, oral
Manufacturer's Standard

Mineralocorticoid for adrenal insufficiency

Endo Operations Ltd.
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Importer/Distributor:
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RECENT MAJOR LABEL CHANGES

None at time of most recent authorization	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLORINEF (fludrocortisone acetate tablets) is indicated:

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

1.1 Pediatrics

Pediatrics (<18 years old): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (>65 years old): No data are available to Health Canada.

2 CONTRAINDICATIONS

FLORINEF is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- with systemic fungal infections.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The lowest possible dose should be used to control the condition being treated, and a gradual reduction in dosage should be made when possible (see 7 WARNINGS AND PRECAUTIONS, General).

4.2 Recommended Dose and Dosage Adjustment

Addison's disease

The recommended oral dose is one tablet (0.1 mg) once daily, although dosage ranging from one tablet (0.1 mg) three times a week to two tablets (0.2 mg) once daily may be used based on individual patient needs.

If treatment-associated hypertension develops, the dose should be reduced to 0.05 mg daily.

Fludrocortisone is preferably administered in conjunction with cortisone (10 to 37.5 mg daily in divided doses) or hydrocortisone (10 to 20 mg daily in divided doses).

Salt-losing adrenogenital syndrome

The recommended oral dose is one tablet (0.1 mg) to two tablets (0.2 mg) once daily.

Pediatrics (< 18 years of age)

Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

4.4 Administration

- FLORINEF is administered orally.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 0.1 mg	Corn starch, dicalcium phosphate, lactose anhydrous, lactose monohydrate, magnesium stearate, sodium benzoate, talc.

FLORINEF tablets are available as white, round, biconvex tablets, scored on one side and with "RPC" over "059" engraved on the other side.

FLORINEF tablets are supplied in bottles of 100 counts.

7 WARNINGS AND PRECAUTIONS

General

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

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

Carcinogenesis and Mutagenesis

Corticosteroids should be used with caution in patients with metastatic carcinoma.

Cardiovascular

Corticosteriods should be used with caution in patients with hypertension, congestive heart failure, thromboembolitic tendencies and thrombophlebitis.

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 high doses. However, since fludrocortisone is a potent mineralocorticoid, both the dosage and salt intake should be

carefully monitored in order to avoid the development of hypertension, edema, or weight gain (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Endocrine and Metabolism

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 and for a year afterwards.

There is an enhanced corticosteroid effect in patients with hypothyroidism.

Corticosteriods should be used with caution in patients with Cushing's syndrome and diabetes mellitus.

Gastrointestinal

Corticosteroids, when used as direct or adjunctive therapy, should be used with caution in patients with diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer (or a history of peptic ulcer) and non-specific ulcerative colitis if there is a probability of impending perforation, abscess, or other pyogenic infection.

Hematologic

Acetylsalicylic acid (ASA) should be used with caution in conjunction with corticosteroids in patients with hypoprothrombinemia.

Hepatic/Biliary/Pancreatic

There is an enhanced corticosteroid effect in patients with cirrhosis.

Immune

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.

Corticosteroids should be used with caution in patients with vaccinia, varicella and antibiotic resistant infections.

If an infection occurs during fludrocortisone therapy, it should be promptly controlled by a suitable therapy.

Fungal infections

Fludrocortisone is contraindicated in patients with systemic fungal infections (see 2 CONTRAINDICATIONS).

Vaccination

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.

Tuberculosis

The use of fludrocortisone 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.

Monitoring and Laboratory Tests

Monitoring of serum electrolytes such as sodium, potassium and calcium is recommended when taking fludrocortisone for an extended period.

Musculoskeletal

Corticosteroids should be used with caution in patients with osteoporosis.

Neurologic

Corticosteroids should be used with caution in patients with convulsive disorders and myasthenia gravis.

Ophthalmologic

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 with caution in patients with ocular herpes simplex because of possible corneal perforation.

Psychiatric

Psychiatric disturbances may appear when corticosteroids are used. These may include euphoria, insomnia, mood swings, personality changes, and severe depression and frank psychotic symptoms. Existing emotional instability or psychotic tendencies may also be aggravated by corticosteroids.

Renal

Corticosteroids should be used with caution in patients with renal insufficiency, acute glomerulonephritis, and chronic nephritis.

Skin

Corticosteroids should be used with caution in patients with exanthema.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled human reproduction studies in pregnant women and women of childbearing potential taking systemic corticosteroids. As such, use of

corticosteroids in this population requires that the possible benefits of the drug be weighed against the potential hazards to the mother or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

7.1.2 Breast-feeding

There are no adequate and well-controlled human reproduction studies in nursing mothers taking systemic corticosteroids. As such, use of corticosteroids in this population requires that the possible benefits of the drug be weighed against the potential hazards to the mother or nursing infant.

7.1.3 Pediatrics

Pediatrics (<18 years old): Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed (see 8 ADVERSE REACTIONS).

7.1.4 Geriatrics

Geriatrics (>65 years old): No data are available to Health Canada.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

When fludrocortisone is used at the recommended small dosages, the side effects seen with cortisone and its derivatives are not usually an issue. However, the following adverse reactions 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:

Table 2 – Potential Adverse Reactions Associated with Systemic Corticosteroids

System Organ Class	Adverse Reactions (Frequency unknown; cannot be estimated from available data)
Cardiac disorders	congestive heart failure (in susceptible patients), syncope, thrombophlebitis
Endocrine disorders	development of the Cushingoid state, increased requirements for insulin or oral hypoglycemic agents in diabetics, glycosuria, hirsutism, manifestations of latent diabetes mellitus, secondary adrenocortical and pituitary unresponsiveness particularly in times of stress (e.g., trauma, surgery, or illness), suppression of growth in children
Eye disorders	exophthalmos, glaucoma, posterior subcapsular cataracts, intraocular pressure increased
Gastrointestinal	abdominal distention, pancreatitis, peptic ulcer with possible

disorders	perforation and hemorrhage, ulcerative esophagitis
General disorders and administration site conditions	impaired wound healing
Infections and infestation	aggravation or masking of infections
Immune system disorders	anaphylactoid reactions
Investigations	blood potassium decreased carbohydrate tolerance decreased, nitrogen balance negative (due to protein catabolism), suppression of reactions to skin tests
Metabolism and nutrition disorders	fluid retention, hyperglycemia, hypokalemic alkalosis, sodium retention
Musculoskeletal, connective tissue and bone disorders	aseptic necrosis of femoral and humeral heads, muscle atrophy, muscle weakness, osteoporosis, pathologic fracture of long bones, spontaneous fractures, steroid myopathy, vertebral compression fractures
Nervous system disorders	convulsions, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo
Psychiatric disorders	insomnia, severe mental disturbances
Reproductive system and breast disorders	menstrual irregularities
Skin & subcutaneous tissue disorders	acneiform eruptions, bruising, ecchymosis, facial erythema, increased sweating, hyperpigmentation of the skin and nails, petechiae, purpura, subcutaneous fat atrophy, striae, thin fragile skin
Vascular disorders	hypertension, necrotizing angiitis

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Interactions with individual behaviour risks such as alcohol consumption, sexual activity and smoking have not been established.

9.4 Drug-Drug Interactions

Caution should be exercised in the concomitant administration of vaccines or immunization procedures (see 7 WARNINGS AND PRECAUTIONS, Vaccination).

Acetylsalicylic acid (ASA) should be used with caution in conjunction with corticosteroids in patients with hypoprothrombinemia.

9.5 Drug-Food Interactions

Interactions with food products have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Corticosteroids may suppress reactions to skin tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Fludrocortisone is a synthetic corticosteroid with potent mineralocorticoid activity. The major effect of mineralocorticoids is the regulation of electrolyte excretion in the kidney.

10.2 Pharmacodynamics

The physiologic action of fludrocortisone is similar to that of hydrocortisone. However, the effects of fludrocortisone, particularly on electrolyte balance, but also on carbohydrate metabolism, are considerably heightened and prolonged. In small oral doses, fludrocortisone 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. In larger doses, fludrocortisone inhibits endogenous adrenal cortical secretion, thymic activity, and pituitary corticotropin excretion, promotes the deposition of liver glycogen and, unless protein intake is adequate, induces negative nitrogen balance.

11 STORAGE, STABILITY AND DISPOSAL

Store refrigerated (2°C and 8°C).

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

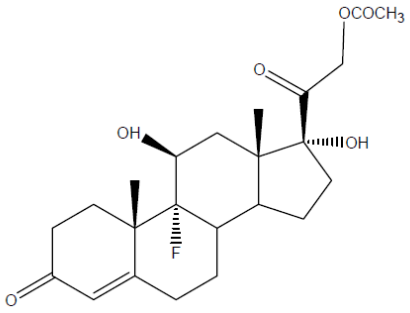
Drug Substance

Proper name: fludrocortisone acetate

Chemical name: 9α-fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione 21-acetate

Molecular formula and molecular mass: $C_{23}H_{31}FO_6$; 422.5 g/mol

Structural formula:



Physicochemical properties: white to practically white, crystalline powder

Solubility: practically insoluble in water

14 CLINICAL TRIALS

The clinical trial data, on which the original indication was authorized, is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

This information is not available for this drug product.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrFLORINEF®

fludrocortisone acetate tablets

Read this carefully before you start taking **FLORINEF** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLORINEF**.

What is FLORINEF used for?

FLORINEF is used to treat:

- addison's disease (also called adrenal insufficiency). This is a condition caused by the adrenal glands in the body not being able to make enough of certain hormones such as cortisol and aldosterone.
- a condition called 'salt losing adrenogenital syndrome'. This occurs when the body is not able to retain enough salt.

How does FLORINEF work?

FLORINEF belongs to a group of medicines called steroids. Steroids occur naturally in the body and help control the balance of water and salt in the body. FLORINEF acts by boosting the body with steroids that retain water and salt in the body.

What are the ingredients in FLORINEF?

Medicinal ingredients: fludrocortisone acetate

Non-medicinal ingredients: corn starch, dicalcium phosphate, lactose anhydrous, lactose monohydrate, magnesium stearate, sodium benzoate, talc

FLORINEF comes in the following dosage forms:

Tablets: 0.1 mg

Do not use FLORINEF if:

- you are allergic to fludrocortisone acetate, or any other steroid medicine, or any other ingredients in FLORINEF.
- you have a fungal infection or any other untreated infection.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLORINEF. Talk about any health conditions or problems you may have, including if you:

- have or have had an infection, such as herpes simplex, chicken pox, tuberculosis.
- have a weak immune response.
- have a cancer that has spread from where it started to another part of your body (metastatic cancer).

- have a high blood pressure.
- have heart problems, such as heart failure.
- have edema (water retention).
- have bleeding problems or blood clotting problems.
- have Cushing's disease (caused by an excess of cortisol hormone).
- have or have had seizures (convulsions) or other neurological problems.
- have myasthenia gravis, a condition that causes progressive muscle pain and weakness.
- have certain eye problem, such as glaucoma, cataract, herpes infection or any problems with the retina.
- have mental health problems, such as depression.
- have diabetes.
- have thyroid problems.
- have liver problems.
- have kidney problems.
- have or have had stomach or gut problems, such as ulcers, ulcerative colitis.
- have low level of potassium or calcium in your blood.
- have brittle bones (osteoporosis).
- have skin rash (exanthema).
- have recently had or are about to have any vaccination.
- are pregnant or trying to become pregnant.
- are breastfeeding or planning to breastfeed.

Other warnings you should know about:

- **Infections**:
  - FLORINEF can make it hard for your body to respond to stress and illness. It can make you more likely to get infections and it can make infections that might be hidden in your body active again.
  - You should avoid coming into contact with people who have measles or chicken pox while taking FLORINEF. If you are exposed, tell your healthcare professional right away.
- **Surgery:** Before you have any operation, tell your healthcare professional that you are taking FLORINEF.
- **Blood Tests:**
  - You may need to take blood tests while on FLORINEF. Your healthcare professional will determine when to perform blood tests and how to interpret the results.
  - Based on the results of your blood tests, your healthcare professional will decide if you should take any dietary supplements or if you need to adjust your diet.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FLORINEF:

- acetylsalicylic acid, used to treat pain and inflammation.

- vaccines.

How to take FLORINEF:

- Take FLORINEF exactly as your healthcare professional tells you to.
- Do not stop taking FLORINEF or change your dose without talking to your healthcare professional. Your healthcare professional will tell you how to reduce your dose gradually when you no longer need to take FLORINEF.

Usual dose:

Your healthcare professional will decide on the dose that is right for you based on your health condition and the progression of the disease.

Overdose:

If you think you, or a person you are caring for, have taken too much FLORINEF, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using FLORINEF?

These are not all the possible side effects you may have when taking FLORINEF. If you experience any side effects not listed here, tell your healthcare professional. nausea

- insomnia
- headache
- spinning sensation (vertigo)
- fainting (syncope)
- slow healing
- darkening of skin or nails
- irregular menstruation
- abnormal hair growth

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN FREQUENCY			
Adrenal suppression: dizziness, nausea, vomiting, abdominal pain, weakness, fatigue, generally feeling unwell, headache		✓	
Allergic reaction: rash, hives, itching, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, skin rash with swelling,			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
itching and large welts, chest pain or tightness			
Blood clots, in the leg or arm: pain, redness and swelling, skin is warm to the touch			✓
Congestive heart failure: shortness of breath with activity or when lying down, fatigue, swelling in the legs, ankles and feet, rapid or irregular heartbeat, cough or wheezing			✓
Cushing's Syndrome (excess cortisol): round "moon face", rapid weight gain especially around the body, excess sweating, thinning of the skin, easy bruising, dry skin, stretch marks, muscle weakness, fat deposits between the shoulder blades (buffalo hump), wounds that are slow to heal		✓	
Diabetes: frequent urination, thirst		✓	
Edema: fluid retention, swelling of the hands, legs or feet		✓	
Eye problems: **Cataracts:** blurry vision, eye pain **Glaucoma:** increased pressure in your eyes, eye pain, halos around lights or coloured images, red eyes **Central serous chorioretinopathy (CSCR):** blurry vision or other changes in vision **Exophthalmos** (bulging of the eye)		✓	
High blood pressure: headaches, feeling unwell, shortness of breath		✓	
Infections: fever, chills, feeling unwell, sore throat, body aches, fatigue			✓
Mental health problems: feeling depressed including thinking about suicide, feeling anxious, insomnia, confusion, hallucinations (seeing or		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
hearing things that are not really there), euphoria (intense feelings of well-being, elation, happiness, excitement and joy), mood swings, personality changes, memory problems			
Muscle weakness/loss		✓	
Osteonecrosis (degradation of bone tissue): progressive or persistent pain or limited range of motion in a joint or limb			✓
Osteoporosis (bone / joint pain, broken bone or weakening of the bones): In situations where healthy people would not normally break a bone you may have sudden pain in any location and especially in the wrist, spine or hip. This may be a broken bone.			✓
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			✓
Seizures: convulsions or fits, with or without loss of consciousness			✓
Skin problems: bruising (red or purplish mark on the skin)		✓	
Stomach ulcers: stomach pain, blood in stools and/or vomiting blood			✓
Slowing of growth in children		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep refrigerated between 2°C and 8°C.
- Keep out of reach and sight of children.

If you want more information about FLORINEF:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the importer/distributor's website, www.paladin-pharma.com or by calling 1-888-867-7426.

This leaflet was prepared by Endo Operations Ltd.

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