SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fludrocortisone acetate 0.1 mg/mL Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of the oral solution contains 0.1 mg fludrocortisone acetate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Clear colourless or slight yellowish, oily liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults:

The recommended daily dose range is: 0.5 ml (0.05mg) to 3 ml (0.3 mg) to be taken once a day. 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 oral solution.

Elderly:

No specific dosage recommendations (See 4.4 Precautions).

Children:

The recommended daily dose range is: 0.5 ml (0.05mg) to 1 ml (0.1mg) to be taken once a day. Caution should be used in the event of exposure to chickenpox, measles or other communicable diseases (See Section 4.3).

Method of administration

Oral use (See section 6.6).

Alternatively, it is also suitable for administration via certain enteral feeding tubes (See section 6.6).

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.

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 antituberculosis 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.

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.

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.

Psychiatric disturbances

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.

Fludrocortisone acetate oral solution is not recommended for administration to patients with swallowing difficulties, owing to the oily nature of the formulation and consequent risks if aspirated.

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.
- 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.
- Ciclosporin: 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: Co-administration may enhance the possibility of digitalis toxicity.
- Oestrogens, include oral contraceptives: Corticosteroid half-life and concentration may be increased and clearance decreased.
- 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 4.4 Special Warnings and Special Precautions for Use.)

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 preeclampsia 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.

Fertility

There are insufficient fertility data available to indicate whether fludrocortisone acetate has any effect on fertility.

4.7 Effects on ability to drive and use machines

None known.

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) and Very rare (< 1/10,000).

System Organ Class	Frequency	MedDRA Terms
Immune system disorders	Unknown*	Anaphylactic reactions, angioedema, rash, pruritus and urticaria, particularly where there is a history of drug allergies. Increased susceptibility and severity of infections with suppression of clinical symptoms and signs
Endocrine disorders	Unknown*	Menstrual irregularities and amenorrhoea; development of the Cushingoid state;
Metabolism and nutrition disorders	Very common	Hypokalaemia
	Uncommon	Hypokalaemic alkalosis; Decreased appetite
	Unknown*	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; latent

		diabetes mellitus and increased requirements for insulin or oral hypoglycaemic agents in diabetes, weight gain. Protein and calcium balance.
Psychiatric disorders	Uncommon	Delusional perception, illusion
		hallucination
	Unknown*	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
Nervous System disorders	Common	Headache
	Uncommon	seizure, epilepsy, syncope, loss of consciousness, dysgeusia
	Unknown*	Insomnia, increased intracranial pressure with papilloedema (pseudo-tumour cerebri) usually after treatment, vertigo, neuritis or paraesthesias and aggravation of pre-existing psychiatric conditions.
Eye disorders	Unknown*	Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases, vision, blurred
Cardiac disorders	Very common	cardiac failure congestive
	Uncommon	Cardiomegaly
Vascular disorders	Very common	Hypertension
Gastrointestinal disorders	Uncommon	Diarrhoea
	Unknown	Dyspepsia, increased appetite peptic ulcer with possible

		subsequent perforation and haemorrhage, pancreatitis, abdominal distension and ulcerative oesophagitis, candidiasis.
Skin and subcutaneous tissue disorders	Unknown*	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.
Musculoskeletal and connective tissue disorders	Common	Muscular weakness
	Uncommon	Muscle atrophy, fatigue, steroid myopathy, 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.
General disorders and administration site conditions	Common	Oedema, swelling, sodium retention, fluid retention, cardiac arrhythmias or ECG changes due to potassium deficiency and increased calcium excretion
Investigations	Uncommon	Blood potassium decreased
	Unknown*	Necrotising angiitis*, thrombophlebitis*, thromboembolism*, leukocytosis*, insomnia and syncopal episodes.
*These adverse reactions have been reported with any corticosteroid therapy		

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).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the 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

Absorption

Fludrocortisone is rapidly and completely absorbed after oral administration.

Biotransformation

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.

Distribution

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.

Elimination

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.

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

There are no additional non-clinical data of relevance to the prescriber that are not stated elsewhere in the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medium Chain Triglycerides

6.2 Incompatibilities

Not known.

6.3 Shelf life

36 months.

After first opening: Use within four months.

6.4 Special precautions for storage

This medicinal product should be stored in the original packaging in order to protect from light.

6.5 Nature and contents of container

Fludrocortisone acetate 0.1 mg/mL oral solution is packed in 60 ml size Type III amber glass bottles and sealed with plastic child-resistant and tamper evident plastic cap (HDPE inside cap body, PP outside cap body, LDPE inside seal top). It contains a 3 ml oral syringe (polystyrene plunger, LDPE plunger piston, LDPE barrel) with 0.1 ml graduations and a neck fitted syringe LDPE adaptor for the bottle.

6.6 Special precautions for disposal

Fludrocortisone acetate 0.1 mg/mL oral solution is provided with a bottle, a cap, a syringe and an adaptor.

Method of administration (oral use)

Fig. 1

Fig. 2

1. The bottle should be shaken well before use and the cap must be removed.

2. When the medicine is used for the first time, the plastic adaptor must be inserted firmly into the bottle neck.
3. The syringe must be inserted firmly into the adaptor. The plunger should be at the bottommost position (Fig. 1).
4. The bottle should be turned upside down in order to fill the syringe. While holding the syringe in place, the plunger should be pulled down gently and the medicine should be drawn to the millilitre (ml) level corresponding to the dose prescribed by your doctor.

Fig 3

5. The bottle should be turned upright again, and the filled syringe must be removed from the adaptor by gentle twisting (Fig. 2).
6. The syringe tip should be inserted into the patient´s mouth and the plunger pressed slowly to release the medicine.
7. After use, the bottle cap must be replaced leaving the adaptor in place.

The syringe should be rinsed and washed with cold or warm water after each use and dried completely before the next use.

For infants and smaller children, drug administration must be performed by parents and professional childcare providers following the instructions:

Follow Steps 1-5 as above.

6. Make sure your child is sitting upright (Fig. 3).
7. Put the tip of the oral syringe inside your child’s mouth between the gums and the inside surface of their cheek.
8. Gently push the plunger to squirt small amounts of medicine into the side of your child’s mouth.
9. Allow your child to swallow before you carry on pushing the plunger. Note: Do not squirt the entire dose into your child’s mouth in one go – they may choke.
10. Give your child a drink to wash down the medicine.
11. After use, the bottle cap must be replaced leaving the adaptor in place.

The syringe should be washed with water after each use and allowed to dry completely before the next use.

Any unused oral solution should be disposed after 4 months after first opening of the bottle. A dosing syringe is provided for accurate measurement of the prescribed dose of the oral solution.

Method of administration (enteral feeding tubes)

Fludrocortisone acetate is suitable for use with the following types of tubes: silicon or polyurethane nasogastric (NG) and percutaneous endoscopic gastrostomy (PEG) tubes of size Fr 13 and Fr 10 respectively with maximum length 120 cm.

Care should be taken during administration due to the oily nature of the product.

It is recommended to administer the drug product following the instructions below:

Ensure that the enteral feeding tube is free from obstruction before administration.

1. The enteral tube should be flushed with water. A minimum flush volume of 10mL is required.
2. The required dose of Fludrocortisone Oral Solution should be administered with a suitable measuring device.
3. The enteral tube should be flushed 3 consecutive times, using a minimum volume of 10mL of water each time.

   Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20646/0092

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25/11/2022

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