1. NAME OF THE MEDICINAL PRODUCT

Fludrace 31.25 micrograms, tablets
Fludrace 62.5 micrograms, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fludrace 31.25 contains 31.25 micrograms fludrocortisone acetate per tablet.
Fludrace 62.5 contains 62.5 micrograms fludrocortisone acetate per tablet.

Excipient(s) with known effect:
Fludrace contains 71.4 mg lactose as lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White round tablet with score line on one side and an inscription on the other side, with a diameter of 6 millimetres.

The 31.25 microgram tablet has the inscription 3. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The 62.5 microgram tablet has the inscription 6. The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fludrocortisone is used as replacement therapy for primary adrenocortical insufficiency (Addison's disease) and for salt-losing congenital adrenal hyperplasia (adrenogenital syndrome), to supplement treatment with a glucocorticoid.

Fludrace is indicated in adults and children aged 2 to 18 years.

4.2 Posology and method of administration

Posology
Primary adrenocortical insufficiency (Addison's disease):
The combination of fludrocortisone with a glucocorticosteroid such as hydrocortisone or cortisone offers a way to achieve optimal substitution.

Adult population:
62.5 µg to 187.5 µg per day. For transient hypertension, 1 tablet a day less.

For congenital adrenal hyperplasia:
62.5 µg to 187.5 µg per day.

Paediatric population
aged 2 years to 18 years: 2-4 tablets of 31.25 µg per day can provide a dosage within the recommended range of 50-150 ug per day. The exact dosing schedule must be titrated individually for each patient.

Method of administration
Take the tablets orally with water.

Paediatric population
This product is suitable for use in children aged 2–18 years. Children who can't swallow the tablets must be treated with a more suitable form of administration.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Ventricular and duodenal ulcer.
- Acute infectious processes; viral infections and systemic fungal infections (bacterial infections: also see section 4.4).
- Tropical helminthic infections
- After vaccination with live attenuated virus (see also section 4.4).

4.4 Special warnings and precautions for use

In principle, corticosteroid therapy should only be used in case of a confirmed diagnosis and if a simpler therapy is not an option or has failed (unless it is a life-threatening situation).
Special caution must be observed in patients who seem to be predisposed to developing complications on the basis of:

- a history of ulcers;
- latent tuberculosis (recent Mantoux result);
- a history of psychiatric disorders:
- osteoporosis;
- hypertension;
- diabetes mellitus.

Corticosteroids may suppress certain symptoms of infection and new infections may occur while using it.
In case of a bacterial infection, the pathogen(s) must be identified first if possible. Then the infections should be treated before starting administration of the corticosteroids.
It is preferable not to administer any vaccinations during corticosteroid therapy.
In case of stress (surgery, trauma, infection) during treatment with corticosteroids and for six months afterwards, there is a risk of acute adrenocortical insufficiency, which may require temporary hydrocortisone prophylaxis.
Regular eye check-ups are highly recommended.
Since fludrocortisone is a strong mineral corticosteroid, both the dosage and the salt intake should be carefully monitored in order to prevent the onset of hypertension, oedema or weight gain.
Concomitant treatment with CYP3A inhibitors, including medicinal products that contain cobicistat, is likely to increase the risk of systemic adverse reactions. This combination must be avoided, unless the benefits outweigh the increased risk of systemic corticosteroid adverse reactions, in which case patients must be monitored for systemic corticosteroid adverse reactions.

Vision disorder
Vision disorder may be reported with systemic and topical use of corticosteroids. If a patient develops symptoms such as blurred vision or other vision disorders, consider referring the patient to an ophthalmologist for an assessment of possible causes, including cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR), which have been reported after use of systemic and topical corticosteroids.

Paediatric population
In order to prevent growth inhibition, an alternating dosing schedule should be the aim in children, even more so than in adults.

4.5 Interaction with other medicinal products and other forms of interaction

Fludrocortisone in combination with loop diuretics, thiazide diuretics or amphotericin B increases the risk of hypokalaemia.
Combination with prostaglandin synthetase inhibitors may have an additive effect on its ulcerogenic potential.
Oestrogens may increase the effect of fludrocortisone.

4.6 Fertility, pregnancy and lactation

Pregnancy
Since fludrocortisone is used as a substitution preparation, stopping or changing this therapy if the patient gets pregnant is not advisable.
There are insufficient data on the use of fludrocortisone during pregnancy in humans to assess its potential harmfulness.
However, the potential risks of corticosteroids to the foetus must be taken into consideration.
Neonates whose mothers used a corticosteroid during pregnancy should be carefully examined for signs of hypo- or hyperadrenalism.

Breast-feeding
There are no data on the excretion of fludrocortisone in human milk.

Fertility
There are no data on the effect of fludrocortisone on male or female fertility.

4.7 Effects on ability to drive and use machines

There are no data on the effect of fludrocortisone on the ability to drive and reaction time.

4.8 Undesirable effects

There are no adverse reactions or complications as such, but corticosteroid therapy does have undesirable inherent effects.

Susceptibility to infections and masking of clinical symptoms
- Decreased resistance, leading to an increased risk of contracting (opportunistic) infections, of unfavourable evolution of infections (sepsis) and of reactivation of latent tuberculosis and of parasitic infections, such as amoebiasis and strongyloidiasis;
- Masking of warning symptoms of sepsis and perforations.

Disruption of fluid and electrolyte balance
- Sodium and fluid retention;
- Cardiac decompensation in predisposed patients;
- Hypertension;
- Potassium depletion with hypokalaemic alkalosis.

Musculoskeletal and connective tissue disorders
- Muscular weakness and muscular atrophy (corticosteroid-induced myopathy);
- Osteoporosis with risk of vertebral compression fractures;
- Aseptic osteonecrosis, especially of the femoral head.

Gastrointestinal disorders
- Peptic ulcer with increased risk of haemorrhage and (masked) perforation;
- Oesophagitis;
- Pancreatitis.

Skin and subcutaneous tissue disorders
- Skin atrophy with high risk of subcutaneous haemorrhage (easy bruising);
- Erythema of the face, acne, hirsutism;
- Impaired wound healing;
- Suppressed skin reaction in skin tests;
- Allergic reactions, such as urticaria.

Nervous system and Psychiatric disorders
- Increased intracranial pressure with papilloedema (pseudotumour cerebri), especially in children during or right after rapid withdrawal;
- Mood changes: euphoria, anxiety, depression;
- Insomnia;
- Psychoses.

Endocrine disorders
- Growth inhibition in children;
- Disruption of the menstrual cycle;
- Inhibition of the hypothalamic-pituitary-adrenal axis (as a result of negative feedback from the exogenous steroid), which may lead to adrenocortical insufficiency if the patient is exposed to stress (trauma, surgery, infection);
- Decreased carbohydrate tolerance, which may lead to the manifestation of latent diabetes or to an increased need for oral blood-glucose-lowering agents or insulin if the patient has known diabetes;
- Onset of Cushing's syndrome.

Eye disorders
- Posterior subcapsular cataract;
- Glaucoma;
- Blurred vision.

Metabolism and nutrition disorders
- Negative nitrogen balance due to protein degradation;
- Centripetal obesity (face, trunk), exacerbated by increased appetite (to be managed with dietary measures).

Other
- Hypersensitivity or anaphylactic reactions;
- Erythrocytosis and granulocytosis, lymphopenia and eosinopenia.

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 the Netherlands Pharmacovigilance Centre Lareb, website: www.lareb.nl.

4.9 Overdose

After a single intake of a high dose of fludrocortisone acetate no effects are expected other than those listed under undesirable effects. Treatment is symptomatic. There are no specific treatment options.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: mineralocorticoids, ATC code: H02AA02.

Fludrocortisone acetate is a synthetic adrenocorticosteroid with strong mineralocorticoid properties that are approximately similar to those of aldosterone. It also has a glucocorticoid effect, but this effect is small compared to its mineralocorticoid effect.
Mineralocorticoids primarily affect water and sodium balance. They promote the reabsorption of sodium in the distal renal tubules, resulting in significant sodium and water retention. They also increase the excretion of potassium and hydrogen ions.
The effect of fludrocortisone on the electrolyte balance (mineralocorticoid effect) is about 100 times stronger than that of hydrocortisone, and its glucocorticoid effect is about 15 times stronger than that of hydrocortisone.
At low oral doses, fludrocortisone causes clear sodium retention and increases the excretion of potassium in urine. Because of its effects on water and sodium balance, fludrocortisone can cause high blood pressure.

5.2 Pharmacokinetic properties

Absorption
Oral administration of fludrocortisone acetate in humans is followed by rapid and complete absorption. Peak plasma concentration is reached in 4 to 8 hours.

Distribution
In humans, 70-80% of the circulating fludrocortisone is bound to plasma proteins.

Biotransformation
After intake, fludrocortisone acetate is quickly hydrolysed to fludrocortisone and other compounds. This happens primarily in the intestines and the liver. Further metabolism takes place primarily in the liver. Approximately 80% of the medicinal product is excreted in urine as polar conjugates. The other 20% is partly excreted in faeces.

Elimination
The plasma half-life after intravenous injection in humans is 30 min. The plasma half-life of fludrocortisone is 3.5 hours or more and the biological half-life is 18 to 36 hours.

5.3 Preclinical safety data

In animals, the only abnormalities that were seen were those associated with the known pharmacological effect. This is the only safety risk for humans based on animal data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Corn starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Fludrace tablets are packaged in an HDPE bottle containing 30 tablets with a PP cap with desiccant.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ace Pharmaceuticals BV.
Schepenveld 41
3891 ZK Zeewolde
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Fludrace 31.25 micrograms, tablets RVG 125017
Fludrace 62.5 micrograms, tablets RVG 50721

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Fludrace, 31.25 micrograms, tablets RVG 125017
Date of first authorisation: 12 July 2022

Fludrace, 62.5 micrograms, tablets RVG 50721
Date of first authorisation: 31 December 1992
Date of latest renewal: 31 December 2012

10. DATE OF REVISION OF THE TEXT

Last partial revision concerns sections: 1, 2, 3, 4.1, 4.2, 6.4 and 8: 12 July 2022