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Public Assessment Report

Scientific discussion

Fludrocortisone acetate Hualan 0.1 mg tablets
Fludrocortisone acetate

SK/H/0281/001/DC

Date: March 2025

This module reflects the scientific discussion for the approval of Fludrocortisone acetate Hualan 0.1 mg tablets. The procedure was finalised on 17 May 2023 (D210). For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fludrocortisone acetate Hualan 0.1 mg tablets, from Hualan Pharmaceuticals Limited, Ireland.

The product is indicated in children above the age of three, adolescents and adults for the treatment of adrenal insufficiency, primary (Addison disease) and congenital adrenal hyperplasia, classic (salt-losing adrenogenital syndrome).

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(a) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as a tablet containing 0.1 mg of fludrocortisone acetate as an active substance.

Tablets are white, round, biconvex tablets, marked "F" on one side, with the other side with a deep break line. The tablet size is 6.0 mm. The tablet can be divided into equal doses.

Tablets are packed in PVC/PE/PVDC-Al blisters available in pack size of 30 tablets.

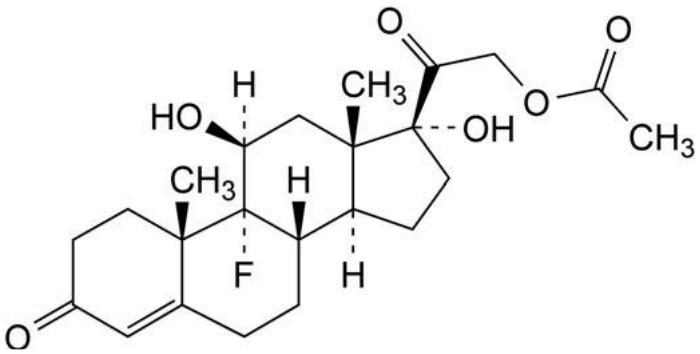
The other ingredients are:

sodium starch glycolate
lactose monohydrate
magnesium stearate

II.2 Drug Substance

Fludrocortisone acetate

Active substance structure:



Empirical formula: $C_{23}H_{31}FO_6$

Chemical name: 9-Fluoro-11β,17-dihydroxy-3,20-dioxopregn-4-en-21-yl acetate.

Appearance: White or almost white, crystalline powder.

Solubility: Fludrocortisone acetate is practically insoluble in water, sparingly soluble in anhydrous ethanol.

Manufacturing: Information on the manufacturing process and process controls has been supplied to, and approved by, the European Directorate for the Quality of Medicines (EDQM) in relation to the Certificate of Suitability Procedure (CEP) for fludrocortisone acetate (Ph. Eur.).

Specifications: The control tests and specifications for drug substance are adequately drawn up. The specification includes adequate test methods in line with the drug substance monograph no. 0767 published in the Ph. Eur.

Stability: Stability studies have been performed with the drug substance and issued by EDQM during CEP procedure. The retest period of fludrocortisone acetate is 60 months if the drug substance is stored at a temperature not exceeding 25 °C in double polyethylene bags, placed in fibre, aluminium or polyethylene containers.

II.3 Medicinal Product

Pharmaceutical development

Pre-formulation studies were carried out including active pharmaceutical ingredient (API) characterisation, compatibility studies with all excipients and stability. The drug substance did not show any incompatibility with each tested excipient. The excipients used in proposed product have Ph. Eur. quality and are commonly used for oral solid preparations.
The development and screening process has identified the final formulation and dry granulation as manufacturing process has been proposed.

Manufacturing

The finished product is manufactured in one strength 0.1 mg using dry granulation. The description of the manufacturing process has been provided in the dossier. Process validation was performed on three batches with size of 100,000 tablets which is the batch size proposed for commercial manufacture.

Specification

The finished product release and shelf-life specifications include appropriate tests and limits for appearance (visual), diameter (in-house), average weight (Ph.Eur.), uniformity of mass of subdivision of tablets (Ph.Eur.), hardness (Ph.Eur.), friability (Ph.Eur.), disintegration (Ph.Eur.), uniformity of dosage units (Ph.Eur.), dissolution (in-house), identification (UV and HPLC, in-house), assay (HPLC, in-house), related substances (HPLC, in-house), and microbiological quality (Ph.Eur.). The finished product specifications cover appropriate parameters for this dosage form in line with ICH Q6A.

Stability

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Stability data were provided for three batches under long-term and accelerated conditions which were packed in PVC/ PE/ PVDC - Al blister (primary packaging). The proposed shelf-life of 36 months without storage conditions to be specified for the drug product was accepted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Adequate data demonstrating quality of this medicinal product were provided in the dossier.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As the medicinal product contains an active substance with well-known properties, the applicant has submitted the marketing authorisation application (MAA) as a bibliographical application pursuant to Article 10(a) of Directive 2001/83/EC as amended. Thus, the dossier contained only references to published scientific literature and no additional non-clinical studies were performed. Further studies were not required.

III.2 Pharmacology

Primary pharmacodynamics

Fludrocortisone is functionally like aldosterone, the body's primary endogenous mineralocorticoid, and is structurally analogous to cortisol, differing only by a fluorine atom at the 9-position of the steroid structure. This fluorination is responsible for fludrocortisone's significant mineralocorticoid potency. Fludrocortisone binding to mineralocorticoid receptors causes alterations to DNA transcription and translation of proteins that result in an increased density of sodium channels on the apical side of renal tubule cells and an increased density of Na^+-K^+-ATPase on the basolateral side. These increases in receptor density result in increased plasma sodium concentrations, and thus increased blood pressure, as well as a decreased plasma potassium concentration.

The applicant presented *in vivo* study in dogs diagnosed with primary and secondary hypoadrenocorticism in which more than 80% of the dogs were considered to have a good to excellent response (fair in 25 (12.5%)) to fludrocortisone acetate therapy. In rats following 30 μg injection of fludrocortisone acetate decrease in sodium excretion was observed and potassium excretion was not significantly changed. Effects of fludrocortisone acetate on water and sodium intake of C57BL/6 mice were investigated by *Johnson et al.* Treatment with fludrocortisone acetate produced dose-dependent (5, 10, and 25 mg/kg) increases in both magnitude and duration of water and sodium intake. In rats, fludrocortisone acetate influenced the spontaneous NaCl intake of adrenalectomized rats.

Secondary pharmacodynamics

The applicant presented the study where the fludrocortisone acetate showed an anti-inflammatory effect as a secondary pharmacodynamic effect in a mouse *otitis media* model.

Safety pharmacology

The data presented in still section covered all vital organ systems. Mainly cardiovascular, gastrointestinal and central nervous system data, and information regarding the absence of respiratory system data, were provided.
In study in cats, it was observed that neither systolic blood pressure nor plasma potassium concentration before and after fludrocortisone suppression differed significantly in either group (non-primary hyperaldosteronism or primary hyperaldosteronism cats). In rats, fludrocortisone acetate induced blood pressure elevation in parallel to an increase of plasma volume. In another study in rats the enlargement of the heart and kidney and atrophy of the spleen and thymus occurred.

Pharmacodynamic drug interactions

Single *i.v.* administrations of fludrocortisone and hydrocortisone increase blood pressure and contractile response of mesenteric arteries to phenylephrine and decrease systemic inflammation. The clinical significance of the interaction between fludrocortisone and hydrocortisone observed in the rat study was discussed. This interaction was deemed not to be clinically relevant.

III.3 Pharmacokinetics

Absorption

Fludrocortisone is rapidly and completely absorbed after oral administration.

Distribution

Fludrocortisone is widely distributed throughout the body. It is 70 to 80% bound to serum proteins, mainly to the globulin fractions. Fludrocortisone can cross the blood-brain barrier and affect the hypothalamic-pituitary-adrenal axis.

Metabolism

Half or more of the substance remained unchanged 30 minutes after *i.v.* or intraduodenal administration in various rodent and non-rodent species. Fludrocortisone is also hydrolysed to non-esterified alcohol.

Elimination

Elimination half-life after *i.v.* administration was 30 minutes in dogs and in human volunteers. Elimination shows triphasic decline. In rats, most of a dose is excreted in the bile, and in dogs and guineapigs most of the dose is excreted in the urine.

Pharmacokinetic drug interactions

Pharmacokinetic interactions between fludrocortisone acetate and barbiturates, phenytoin, and rifampin were discussed. These substances enhance the metabolism and reduce the effects of fludrocortisone acetate. Oral contraceptives may increase plasma concentrations.

III.4 Toxicology

Single dose toxicity

Presented LD_{50} values of doses given intraperitoneally to mice and orally to rats were 240 mg/kg and more than 1,000 mg/kg, respectively. Safety factors determined to be more than 50.

Repeat dose toxicity

The toxicity after repeated dosing was established in mouse, rat (rodent) and cat, dog (non-rodent) model with limited incorporation of toxicokinetic in the design on studies. No critical harm has been identified in the presented studies.

Genotoxicity

Fludrocortisone acetate was not genotoxic in both presented *in vitro* chromosomal aberration and sister chromatid exchange (SCE) assay. Corticosteroids prevented the induction of gene mutation in a bacterial mutagenicity assay, the induction of chromosomal aberration by hydrocortisone and dexamethasone *in vitro* in human lymphocytes and *in vivo* in mice and exerted the negative results of the fludrocortisone chromosomal aberration test in human lymphocytes. Taking into consideration all

publicly available genotoxicity data, mutagenic effects of this corticoid with predominantly mineralocorticoid activity are unlikely.

Carcinogenicity

Adequate studies in animals have not been performed. There is no information on the carcinogenicity of fludrocortisone, and a 2-year study on rats found no evidence of the carcinogenic effects of other corticosteroids. As a result, there are no concerns raised regarding the carcinogenicity of this well-known drug substance.

Reproductive and developmental toxicity

Adequate animal reproduction studies have not been conducted with fludrocortisone acetate. Corticosteroids have been shown to be teratogenic in many species and yielded an increased incidence of malformations, embryo-foetal lethality and intra-uterine growth retardation. In addition, corticosteroids reduced fertility in male rats. Fludrocortisone affected uterine receptivity.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The applicant provided consumption statistics covering the period of 4 years (2019-2022) in Slovakia. These data have not shown a significant increase in fludrocortisone consumption in RMS. The highest consumption was reported to be in 2021.

A measured logP value of 1.67 from a research article was submitted by the applicant. Because the experimental method was not specified in this article, the applicant chose to confirm this value by carrying out a relevant experiment and submitting it as a post-authorisation variation.

As part of Phase I, PECsw was calculated using refined Fpen based on the prevalence data. The PECsw value calculated only for Addison disease prevalence was above the action limit.
PECsw calculation was also provided using the default Fpen value and the maximum daily dose for Addison disease and for salt-losing adrenogenital syndrome. PECsw values for respective indications were determined and these values are summed for a total PECsw value of 0.0025 µg/L, which is below the action limit.

The risk characterisation ratio was calculated as PECsw/PNEC to give a value < 1. The risk characterisation ratio would be below the action limit in the case of both PECsw calculations. Therefore, it was concluded that the use of the medicinal product containing fludrocortisone is unlikely to pose environmental risks.

III.6 Discussion on the non-clinical aspects

In overall, non-clinical overview was of appropriate quality for a chosen legal basis – bibliographic application pursuant to Article 10a of Directive 2001/83/EC. Adequate references to published scientific literature covering pharmacodynamic and pharmacokinetic properties of fludrocortisone together with data on its safety and toxicity were provided.

Nevertheless, some aspects related to ERA were committed to be fulfilled post-authorisation (the logP experiment).

IV. CLINICAL ASPECTS

IV.1 Introduction

This MAA was submitted based on scientific bibliographical evidence supporting the risk-benefit profile for fludrocortisone acetate and provides adequate justification for the marketing approval of the

product. A literature review was undertaken to identify and retrieve relevant research articles describing the clinical pharmacology, efficacy and the safety profile of fludrocortisone acetate.

IV.2 Pharmacokinetics

Fludrocortisone is rapidly and completely absorbed after oral administration. 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 cerebrospinal fluid to that in plasma was 1:6 in human volunteers. Fludrocortisone is hydrolysed to produce the non-esterified alcohol; after administration of the acetate, only the non-esterified alcohol is detectable in blood. Maximal plasma concentration of fludrocortisone occurs 90 to 120 minutes after intake and mean plasma half-time is 4.9 hours. Fludrocortisone is mainly excreted in urine (Anonymous/3-5; Esposito D, et al., 2018; Rahman M, et al., 2021).
Fludrocortisone plasma concentrations and effect on urinary sodium/potassium ratio had a higher inter-individual variability as compared to hydrocortisone (Hamitouche N, et al., 2017).

IV.3 Pharmacodynamics

Fludrocortisone is synthetic mineralocorticoid which acts as main endogenous mineralocorticoid, aldosterone. The physiologic action of fludrocortisone acetate is like that of hydrocortisone. However, the effects of fludrocortisone acetate, particularly on electrolyte balance, but also on carbohydrate metabolism, are considerably heightened and prolonged. Mineralocorticoids act on the distal tubules of the kidney to enhance the reabsorption of sodium ions from the tubular fluid into the plasma; they increase the urinary excretion of both potassium and hydrogen ions. In small oral doses, fludrocortisone acetate 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 acetate 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 (Anonymous/3-6; Esposito D, et al., 2018; Goonaratna C de FW, et al., 1975; Rahman M, et al., 2021; Samuel S, et al., 2017).

Fludrocortisone acetate (9-α-fluorohydrocortisone), evaluated in several clinical conditions to compare its effect with cortisone and desoxycorticosterone acetate, was shown to have a cortisone-like effect averaging 15- to 20-times as great as hydrocortisone in its ability to:
(1) inhibit the pituitary stimulation of the adrenal cortices.
(2) produce loss of nitrogen, calcium, and phosphorus.
(3) inhibit inflammation.
(4) produce a sense of well-being.
Fludrocortisone acetate influences mineral and water metabolism like desoxycorticosterone but averaging about five times as great as desoxycorticosterone in its ability to promote sodium, chloride, and water retention and potassium diuresis. Its greatest clinical usefulness is replacement therapy in adrenal insufficiency or adrenal surgery where both desoxycorticosterone and cortisone effects are desirable (Hamwi GJ, et al., 1955). Fludrocortisone suppresses sympathetic nerve activity in humans (Mion D Jr, et al., 1994).

IV.4 Clinical efficacy

The starting fludrocortisone dose consists of 0.05 to 0.1 mg daily in the morning, as physiological aldosterone secretion follows a circadian rhythm like that of cortisol, with peaks at 8:00 AM and ends at 11:00 PM, which is then titrated in steps of 0.025 to 0.05 mg. A higher dose (up to 0.5 mg daily) is needed in newborns and children, because their mineralocorticoid sensitivity is lower compared with adults, as well as in the last trimester of pregnancy, when high levels of progesterone may counteract the effects of mineralocorticoids. Otherwise, dose adjustments are rarely recommended, but this should probably be done more often. Temporary dose increments of 50% to 100% may however be recommended in hot climates and conditions that promote excessive sweating, such as long-lasting exercise. A Swedish population-based observational study reported that mineralocorticoid replacement

was used by 89% of all patients with PAI, with a median fludrocortisone dose of 0.1 mg/d (range, 0.014 to 1.0 mg/d). Previous analysis of 664 patients with PAI from Norway had shown that the mean dose of fludrocortisone was 0.1 mg/d. The available forms of fludrocortisone preparation include 0.1 and 0.05-mg tablets (Esposito D, et al., 2018).
The required amount of mineralocorticoids is closely related to the intake and loss of electrolytes. The fludrocortisone dosage is evaluated clinically by the assessment of blood pressure in the lying and supine position, and the presence of salt craving and oedema. The dosage is further guided by the measurement of the Na+ and K+ homeostasis. The recommended target level for plasma renin activity (PRA) is at or slightly above the upper normal reference limit (Anonymous/3-6; Løvås K, et al., 2003; Rahman M, et al., 2021).

IV.5 Clinical safety

The various reported side effects of fludrocortisone acetate 0.1 mg tablets are as follows:

- Anti-inflammatory and immunosuppressive effects: Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (Anonymous/3-6; Løvås K, et al., 2003; Warne G, 2008).

- Fluid and electrolyte disturbances: Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, cardiac arrhythmias or ECG changes due to potassium deficiency, hypokalaemic alkalosis, increased calcium excretion and hypertension (Anonymous/3-6; Bhattacharyya A, et al., 1998; Bonfig W, et al., 2014; Burns A, et al., 1983; Castinetti F, et al., 2017; Esposito D, et al., 2018;Husebye ES, et al., 2014; Hussain RM, et al., 1996; Løvås K, et al., 2003; Warne G, 2008; Willis FR, et al., 1994).

- Musculoskeletal: Muscle weakness, fatigue, steroid myopathy, loss of muscle mass, 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 (Anonymous/3-6; Warne G, 2008).

- Gastrointestinal: Dyspepsia, peptic ulcer with possible subsequent perforation and haemorrhage, pancreatitis, abdominal distension and ulcerative oesophagitis, candidiasis (Anonymous/3-6; Warne G, 2008).

- Hypersensitivity: Anaphylactic reactions, angioedema, rash, pruritus and urticaria, particularly where there is a history of drug allergies (Anonymous/3-6; Kato J, et al., 2011; Warne G, 2008).

- Dermatologic: 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 (Al Jurayyan NAM, et al., 2016; Anonymous/3-6; Løvås K, et al., 2003; Warne G, 2008).

- Neurological: Euphoria, psychological dependence, depression, insomnia, convulsions, increased intracranial pressure with papilloedema (pseudo-tumour cerebri) usually after treatment, vertigo, headache, neuritis or paraesthesias and aggravation of pre-existing psychiatric conditions and epilepsy (Al Jurayyan NAM, et al., 2016; Anonymous/3-6; Hussain RM, et al., 1996; Warne G, 2008).

- Endocrine/metabolic: Menstrual irregularities and amenorrhoea; development of the Cushingoid state; 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; manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycaemic agents in diabetes, weight gain. Negative protein and calcium balance. Increased appetite (Al Jurayyan NAM, et al., 2016; Anonymous/3-6; Warne G, 2008).

- Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, papilloedema, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases (Anonymous/3-6; Warne G, 2008).

- Others: Necrotising angiitis, thrombophlebitis, thromboembolism, leucocytosis, insomnia and syncopal episodes (Anonymous/3-6; Warne G, 2008).

- Eye disorders: Vision, blurred (Anonymous/3-6; Warne G, 2008).

- 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 (Anonymous/3-6; Warne G, 2008).

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fludrocortisone acetate Hualan 0.1 mg tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

IV.7 Discussion on the clinical aspects

From a clinical point of view, the application contained adequate clinical data that supported chosen legal basis – bibliographic application.

During the procedure issue concerning the use of the proposed medicinal product in children under three years of age and suitability of a chosen pharmaceutical form – tablet – was discussed.
The indications and respective diseases as presented and approved in section 4.1 of the SmPC may occur in children under 3 years of age (i.e., newborns) and the solid pharmaceutical formulation (i.e., tablet) is not suitable for this age group. This can lead to an off-label use in cases under 3 years of age. From the safety perspective, the pharmaceutical formulation was not considered safe for the paediatric population under 3 years of age. The administration of fludrocortisone acetate under this age, would only be possible if there was enough data suggesting that the manipulation of this pharmaceutical formulation will not change the pharmacokinetic in this population.

Therefore, indication has been restricted for children from 3 year of age and the potential use in children younger than 3 years remained to be solved in the post-authorisation phase.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This was an MAA of medicinal product for human use as it is defined in Article 10(a) (bibliographic application) of the European Directive 2001/83/EC as amended. Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS. The applicant, Hualan Pharmaceuticals Limited, Ireland, has submitted this MAA under procedural number SK/H/0281/001/DC.

From a (non-)clinical point of view, the application contained adequate clinical data that supported chosen legal basis – bibliographic application. Issues concerning the use of the proposed medicinal product in children under three years of age and ERA remain to be solved in the post-authorisation phase.

Quality aspects of the dossier were adequately described; specifications of API fludrocortisone acetate were in line with monograph no. 0767 published under Ph. Eur. and that of finished medicinal product in line with ICH Q6A.

There was no discussion in the CMDh. Agreement between the member states was reached during a written procedure. Based on submitted data referring to published scientific literature applicant adequately addressed the requirements for a bibliographical application pursuant to Article 10(a) and sufficiently demonstrated the quality of a medicinal product in the scope of this MAA. Therefore, the member states granted the marketing authorisation. This decentralised procedure was positively concluded on 17 May 2023 (D210).

VI.1 Proposed list of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

The applicant committed to complete ERA and submit the results of the on-going experimental studies to calculate the logP for fludrocortisone acetate as a post-authorisation measure.

LIST OF REFERENCES

Anonymous (2014): Adrenal insufficiency -a guide for pharmacists and their teams by Auden Mckenzie (Pharma Division) Ltd. June 2014 - ADV 10079

Anonymous (2017): Summary of Product Characteristics - Fludrocortisone acetate 0.1 mg tablets by Aspen Pharma Trading Limited

Anonymous (2019): Fludrocortisone Acetate- fludrocortis one acetate tablet. Teva Pharmaceuticals USA, Inc.

Anonymous (2020): glucocorticoid_pharmacology [TUSOM | Pharmwiki]

Bhattacharyya A, et al., (1998): Heart failure with fludrocortisone in Addison's disease. J R Soc Med. 1998 Aug;91(8):433-4.

Bonfig W, et al., (2014): Blood pressure, fludrocortisone dose and plasma renin activity in children with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency followed from birth to 4 years of age. Clin Endocrinol (Oxf). 2014 Dec;81(6):871-5.

Burns A, et al., (1983): Extreme metabolic alkalosis with fludrocortisone therapy. Postgrad Med J. 1983 Aug;59(694):506-7.

Castinetti F, et al., (2017): 4: Replacement therapy for adrenalin sufficiency. Annalesd'Endocrinologie, ElsevierMasson, 2017;78(6): 525-534.

Esposito D, et al., (2018): Primary Adrenal Insufficiency: Managing Mineralocorticoid Replacement Therapy. J Clin Endocrinol Metab, February 2018, 103(2):376–387.

Goonaratna C de FW, et al., (1975): Assessment of urine-concentrating ability in man: effect of fludrocortisone and urea in enhancing response to vasopressin. Clin Sci Mol Med. 1975 Apr;48(4):269-78.

Hamitouche N, et al., (2017): Population Pharmacokinetic-Pharmacodynamic Model of Oral Fludrocortisone and Intravenous Hydrocortisone in Healthy Volunteers. AAPS J . 2017 May;19(3):727-735.

Hamwi GJ, et al., (1955): Clinical use of fludrocortisone acetate; preliminary report. J Am Med Assoc. 1955 Dec 24;159(17):1598-601.

Husebye ES, et al., (2014): Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014 Feb;275(2):104-15.

Hussain RM, et al., (1996): Fludrocortisone in the treatment of hypotensive disorders in the elderly. Heart. 1996 Dec;76(6):507-9.

Kato J, et al., (2011): Hypersensitivity to fludrocortisone acetate in a recipient of bone marrow transplantation. Allergol Int. 2011 Dec;60(4):557-8.

Løvås K, et al., (2003): Replacement therapy in Addison's disease. Expert Opinion on Pharmacotherapy, 2003; 4:12, 2145-2149.

Mion D Jr, et al., (1994): Effects of fludrocortisone on sympathetic nerve activity in humans. Hypertension. 1994 Jan;23(1):123-30.

Rahman M, et al., (2021): Fludrocortisone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2021 Jan 26.

Samuel S, et al., (2017): Pharmacologic Characteristics of Corticosteroids. J Neurocrit Care 2017;10(2):53-59.

Warne G (2008): Application for inclusion of Fludrocortisone tablets in the WHO. Model List of Essential Medicines for Children. (July 2008).

Willis FR, et al., (1994): Fludrocortisone induced heart failure in Addison's disease. J Paediatr Child Health. 1994 Jun;30(3):280-1.