COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fludrocortisonacetaat Helm 0.1 mg/ml oral solution
(fludrocortisone acetate)

(NL/H/5300/001/DC)

Date: 24 February 2023

This module reflects the scientific discussion for the approval of Fludrocortisonacetaat Helm 0.1 mg/ml oral solution. The procedure was finalised at 23 December 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

11 β-HSD2	11 β-hydroxysteroid dehydrogenase type 2
11-DOC	11-deoxycorticosterone
ASMF	Active Substance Master File
BP	Blood pressure
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CO	Cardiac output
DBP	Diastolic blood pressure
DHEA	Dehydroepiandrosterone
DOCA	Deoxycorticosterone acetate
DOPS	Dihydroxyphenylserine
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ESC	European Society of Cardiology
FD	Familial dysautonomia
HUT	Head-up tilt
ICH	International Conference of Harmonisation
IPD	Idiopathic Parkinson's Disease
MAH	Marketing Authorisation Holder
MR	Mineralocorticoid receptor
NOH	Neurogenic orthostatic hypotension
OH	Orthostatic hypotension
PI	Prostaglandin inhibition
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PV	Plasma volume
RCT	Randomised controlled trial
RH	Relative Humidity
RMP	Risk Management Plan
SBP	Systolic blood pressure
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fludrocortisonacetaat Helm 0.1 mg/ml oral solution, from Helm AG.

Fludrocortisonacetaat Helm is indicated:
- as replacement therapy in case of mineralocorticoid deficiency, adjunctive to glucocorticoid therapy (in all age groups),
    - in primary adrenal insufficiency (Addison's disease) and
    - salt-wasting congenital adrenal hyperplasia.
- as short-term treatment of severe orthostatic hypotension requiring pharmacologic treatment in all age groups. Fludrocortisone acetate oral solution is only indicated if general and physical measures are not sufficient and duration of treatment should be restricted to the shortest period possible.

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

The MAH also applied for an indication of secondary adrenocortical insufficiency, but this was dropped during the procedure, as it was not in line with the indications of the reference product and it was not sufficiently supported in provided literature (see section *IV.4 Clinical efficacy*).

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Florinef Acetaat, tablets 0.1 mg (NL RVG 07897) which has been registered in the Netherlands by Mylan Healthcare B.V. since 1980 (original product). The new product differs from the innovator product in pharmaceutical form and indication.

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

<u>Assessment of similarity with authorised orphan medicinal product(s) under market exclusivity</u>
Having considered the arguments presented by the MAH and with reference to Article 8 of Regulation (EC) No 141/2000, Fludrocortisone 0.1 mg/ml oral solution is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Plenadren. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Plenadren in the treatment of adrenal insufficiency in adults does not prevent the granting of the marketing authorisation of Fludrocortisonacetaat Helm. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Introduction

Fludrocortisonacetaat Helm is a clear, colourless or slight yellowish, oily liquid and the product contains as active substance 0.1 mg of fludrocortisone acetate per mL.

The oral solution is packed in a 60 mL type III amber glass bottles and sealed with a plastic child-resistant and tamper evident cap. It contains a 3 mL oral syringe with 0.1 mL graduations and a neck fitted syringe adaptor for the bottle.

The excipient included in this formulation is medium chain triglycerides.

II.2 Drug Substance

The active substance is fludrocortisone acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is white or almost white, crystalline powder and is practically insoluble in water, sparingly soluble in ethanol and chloroform and slightly soluble in ether. The dissolved state of the drug substance in the finished product negates the effect of polymorphism. Hence, no impact on the manufacturability, overall quality and *in vivo* performance is anticipated.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP. Additionally, a microbiological quality test is included in line with the requirements for an oral drug product. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 5 years when stored in the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Since the product concerns an oral solution, no comparative dissolution test are applicable.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The manufacturing process is a standard process and consists of dissolving. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients complies with the Ph.Eur. monograph. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, deliverable volume, assay, related substances, uniformity of mass of delivered doses from multidose container and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf life specifications are identical. The analytical methods have been adequately described. The test procedures for assay, dissolution and impurities have been validated. Satisfactory validation data for these analytical methods have been provided. A forced degradation study was performed, confirming that the method for assay and related substances are stability indicating. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches for 24 months at long term (25°C/60% RH), 12 months at intermediate conditions (30°C/65% RH) and for 6 months at accelerated conditions (40°C/75% RH), in accordance with applicable ICH guidelines, demonstrating the stability of the product for 36 months. On basis of the data submitted, a shelf life of 36 months was granted. A photostability study demonstrated that the drug product is sensitive to light and therefore, the drug product should be stored in the original container in order to protect from light.

An in-use stability study was performed (stored in upright and inverted position) at the beginning of shelf-life at room temperature. No change in any of the investigated parameters was observed. The proposed shelf-life after first opening of 4 months is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fludrocortisonacetaat Helm has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

An environmental risk assessment Phase I is completed. The PEC_{sw} is 0.0015 µg/L, which is below the action limit of 0.01 µg/L. However, as the active substance fludrocortisone is a hormone that may affect the development and reproduction of animals, a Phase II assessment would be warranted if an increase in environment exposure is expected when the market authorisation is granted. Since Fludrocortisonacetaat Helm is intended for hybrid substitution, the MAH intends to prove post-approval that this market authorisation will not lead to an increased exposure to the environment, and if this cannot be proven, a fish full life cycle will be performed.

Table 1. Results of the environmental risk assessment

Substance (INN/Invented Name): fludrocortisone					
CAS-number (if available): 514-36-3 (fludrocortisone acetate)					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.24			Not B
PBT-statement :	fludrocortisone is not PBT, nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default	0.0015	mg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)		Potential endocrine disruptor			(Y)
Phase IIa Effect studies - Tailored					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Fish Short Term Reproduction Assay with modifications / *Danio rerio*	OECD 229, modified	NOEC	≥42	µg/L	fecundity
Fish full life cycle test		NOEC/ECx	TBD	µg/L	TBD

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Florinef Acetaat, tablets 0.1 mg which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology and pharmacokinetics data. Therefore, the member states agreed that no further non-clinical studies are required.

The following post-approval commitment was made:

- The MAH agrees to document through the submission of a post-approval measure/variation, that the consumption of the active substance, based on actual sales data from Fludrocortisonacetaat Helm 0.1mg/ml oral solution and from the reference product in the territories concerned by these procedures, is not significantly increased upon entry of the hyrbid product in the market (deadline 3 years). Alternatively, a fish full life cycle should be performed (deadline 5 years).

IV. CLINICAL ASPECTS

IV.1 Introduction

Fludrocortisone acetate is a well-known active substance with an established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required. For this hybrid application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fludrocortisonacetaat Helm 0.1 mg/ml oral solution (Helm AG, Germany) is compared with the pharmacokinetic profile of the reference product Florinef Acetaat, tablets 0.1 mg (Mylan Healthcare B.V., The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions with the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

<u>Bioequivalence studies</u>

Design

A randomised, open-label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male

subjects, aged 20-44 years. Each subject received a single dose (0.1 mg) of one of the two fludrocortisone acetate formulations. The oral solution (test product) and the tablet (reference product) were orally administered with 240 mL water after a fasting period of 10 hours. There were two dosing periods, separated by a washout period of 13 days.

Blood samples were collected at pre-dose and at 0.083, 0.16, 0.25, 0.5, 0.75, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24 and 48 hours after administration of the products.

The design of the study is acceptable.

Fludrocortisone acetate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of fludrocortisone acetate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Out of a total of 40, 38 subjects were eligible for pharmacokinetic analysis. In period II, one subject was withdrawn because of misbehaviour towards the staff and one subject withdrew due to personal reasons.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fludrocortisone acetate (0.1 mg) under fasted conditions

Treatment N=38	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	3166.30	3278.89	857.78	0.83 (0.50 – 2.50)
Reference	3195.79	3311.48	990.06	0.50 (0.50 – 1.50)
***Ratio (90% CI)**	0.99 (0.96 – 1.02)	0.99 (0.96 – 1.02)	0.87 (0.81 – 0.93)	-
Intra CV (%)	7.15	7.09	17.71	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CI confidence interval
CV coefficient of variance

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Fludrocortisonacetaat Helm is considered bioequivalent with Florinef Acetaat.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Pharmacodynamics

Adrenocortical insufficiency

Addison's disease was first described by Thomas Addison in 1855, who attributed the disease to loss of adrenal function. Addison's disease has thus become the notation for primary adrenal insufficiency. Symptoms can include fatigue, hypotension and dizziness, abdominal pain, muscle weakness, headaches and more. The adrenals produce steroid hormones, i.e., corticosteroids (mineralocorticoids, glucocorticoids and adrenal androgens) in the cortex and catecholamines (mainly adrenaline) in the medulla. The syndrome is caused by deficiency of these hormones, of which the mineralocorticoids and glucocorticoids are essential for life. At the time of clinical diagnosis, aldosterone levels will usually be low, leading to hyperkalaemia, hyponatraemia, elevated renin levels, and reduction of adrenal androgen dehydroepiandrosterone (DHEA) and its sulphate ester DHEAS. Aldosterone plays a key role in the homeostasis of water and electrolytes. The principal stimulators of aldosterone synthesis and secretion are angiotensin II and potassium. Aldosterone shows diurnal variation with an early night-time decline and late-night rise that is likely to result to a large extent from diurnal variation in renin activity. Aldosterone binds to the mineralocorticoid receptor (MR), a nuclear receptor which is expressed mainly in the kidneys, colon and salivary glands but also to some extent by liver, brain, pituitary gland and peripheral blood mononuclear cells. Activation of the MR results in gene regulation which promotes sodium reabsorption and potassium excretion in these organs. Cortisol and aldosterone bind to the MR with similar affinity but cortisol is inactivated (i.e., oxidised) locally in mineralocorticoid target tissues by the enzyme 11 β-hydroxysteroid dehydrogenase type 2 (11 β-HSD2). Most patients with Addison's disease require mineralocorticoid replacement, whereas mineralocorticoids do not usually have to be replaced in secondary adrenal failure. The natural mineralocorticoids aldosterone and 11-deoxycorticosterone (11-DOC) are difficult to synthesise and have a short half-life, respectively. Therefore, in clinical practice, the synthetic mineralocorticoid fludrocortisone is used. The glucocorticoid replacement contributes to the mineralocorticoid effect, depending on glucocorticoid type and dose and possibly variable activity of the 11 β-HSD2 enzyme (Lovas, 2008).

Orthostatic hypotension

Fludrocortisone acetate alters blood pressure through a variety of mechanisms, including mineralocorticoid-induced sodium and water retention. Fludrocortisone binds to the aldosterone receptor, which increases activity of the distal tubule of the kidney, causing enhanced sodium ion and water transport into the plasma, and increasing urinary excretion of potassium and hydrogen ions (Cambell, 1975). Its effect on alleviating orthostatic hypotension is largely thought to be modulated through these actions. With chronic use, a

blood pressure-raising effect may persist, even though sodium retention and overall plasma volume normalises through increased peripheral vascular resistance (Chobanian, 1979; Armstrong, 1991; Hoeldtke, 1993; Freeman, 2003). Other potential mechanisms may include sensitisation of the vasculature to angiotensin II and norepinephrine (Hickler, 1959) (Lieshout, 1993). Because orthostatic hypotension is a condition that results from multiple underlying diseases and conditions, it is important to analyse the effect of fludrocortisone by mechanism (peripheral versus central autonomic failure), by condition (Parkinson's Disease, diabetes, amyloid-induced orthostatic hypotension, pure autonomic failure, Lewy body disease, or multiple system atrophy), and by age, as both the benefits and potential for harm may vary between subgroups. As an example, the blood pressure-raising properties of fludrocortisone could potentially increase the risk of supine hypertension in certain subgroups, particularly the elderly (Veazie, 2017).

IV.4 Clinical efficacy

Replacement therapy

Fludrocortisone acetate is widely used as therapy in case of mineralocorticoid deficiency, adjunctive to glucocorticoid therapy. In 1955, fludrocortisone acetate and hydrocortisone (given orally) were shown to be an effective treatment for patients with Addison's disease. All patients on this combined therapy were adequately controlled and showed no signs of hypernatremia when the recommended doses were employed (Kupperman, 1955). Smith (1984) described that an adequate dose of fludrocortisone treatment was necessary to maintain adequate sodium and water balance in Addison's disease patients.

The MAH applied for an indication of replacement therapy in case of secondary adrenocortical insufficiency, but this was dropped as it was not in line with the reference product and it was not sufficiently supported. In most patients with secondary adrenal insufficiency, mineralocorticoid replacement therapy is not necessary. Primary adrenal insufficiency is associated with both cortisol and mineralocorticoid deficiency. In contrast, secondary and tertiary adrenal insufficiency are associated with cortisol, but not mineralocorticoid deficiency, because aldosterone is regulated primarily by the renin-angiotensin system, which is independent of the hypothalamus and pituitary.

Orthostatic hypotension

The European Society of Cardiology (ESC) guideline (Moya, 2009) defines postural or orthostatic hypotension (OH) as 'an abnormal decrease in systolic blood pressure (BP) upon standing', leaving the level of BP fall in mmHg unstated. It has also been arbitrarily defined as a fall in systemic arterial systolic blood pressure (SBP) of 20 mmHg and/or a reduction in diastolic BP (DBP) of 10 mmHg when standing from a supine or sitting position with or without symptoms (Lahrmann, 2006). Postural hypotension can cause a variety of symptoms including dizziness, light-headedness and falls. However, despite being asymptomatic in some people, it is associated with an increased risk of mortality (Davis, 1987).

There have been numerous clinical studies published in the literature reporting benefits after the use of fludrocortisone in the symptomatic treatment of orthostatic hypotension, these are listed in Table 3 below.

Table 3. Summary of literature regarding efficacy in orthostatic hypotension

Author	Content
Owen, 1957	Case reports (N=4). Fludrocortisone raised the BP in an infant with adrenogenitalism and 3 patients with Addison's disease.
Hickler, 1959	Case report (N=1). Fludrocortisone raised the BP in a patient with primary autonomic insufficiency.
Schirger, 1962	N=6, idiopathic OH; initially 1mg fludrocortisone BD, maintenance dose 0.5-1mg OD or BD; follow-up 8-24 months. Fludrocortisone raised the BP in 5 patients, 1 patients developed an increased sodium retention and potassium excretion.
Schatz, 1963	N=40, 29 with idiopathic OH, 11 with diabetic OH. Dose fludrocortisone 0.1 to 0.4mg daily; follow-up 5-18 months. Unclear how many patients received fludrocortisone. 5 patients improved, 1 partially improved.
Frick, 1966	N=3, postural hypotension. Fludrocortisone raised the BP and relieved symptoms in 2 out of 3 patients.
Sear, 1968	N=6, 2 DM OH, 3 idiopathic OH, 1 atherosclerosis. Fludrocortisone raised the BP in all 6 patients. Fludrocortisone given together with the salt provided further improvement.
Bannister, 1969	N=4, OH. Fludrocortisone raised the BP in all 4 patients.
Hoehn, 1975	N=6, OH secondary to levodopa therapy; initially 0.05mg fludrocortisone OD, daily dosage was increased by 0.05 mg each week until symptoms were relieved. Fludrocortisone raised the BP in all 6 patients.
Campbell, 1975	Crossover, N=6, DM OH. Fludrocortisone 0.1 mg BD; follow-up 3 weeks. Fludrocortisone improved symptoms in 4 out of 6 patients. 2 patients with a low albumin reported ankle oedema, 1 patient headache and breathlessness.
Campbell, 1976	N=14, DM OH. Fludrocortisone range 0.1-0.4mg; follow-up range of 6-30 months. Fludrocortisone improved BP and symptoms in 13 out of 14 patients, in 1 patient BP improved but symptoms remained partly.
Davidson, 1976	N=1, idiopathic OH, compared to 5 other patients. Follow-up 6 weeks. Fludrocortisone improved the clinical response.
Schatz, 1976	N=23, OH with variable aetiology. Fludrocortisone 0.1-0.5mg OD, mean follow-up 25.7 months. Fludrocortisone resulted in a satisfactory response in 18 out of 23 patients. Five out of 23 patients developed recumbent hypertension, fluid retention or congestive heart failure.
Watt, 1981	N=5. Treatment with fludrocortisone and flurbiprofen raised the BP in all 5 patients.
Matsubara, 1990	N=7, central neurogenic OH. Fludrocortisone 0-2mg and DOPS therapy. Fludrocortisone plus DOPS treatment improved the BP in all patients. One patient developed congestive heart failure.
Harkel, 1992	N=6, 5 patients were treated with sleeping with a head-up tilt position and fludrocortisone.

Balaji, 1994	N=162, neurocardiogenic syndrome in children 1-20 year old. 1st choice fludrocortisone 0.1mg plus salt. 2nd choice metoprolol. Treatment 6 months, follow-up 12 months. Fludrocortisone plus salt resulted in success rate of 65%, 17% of patients had some improvement. Five patients developed an AE: 3 headache, 1 facial swelling, 1 transient hypertension.
Dacosta, 1993	N=11, elderly with OH due to vasodepressor carotid sinus syndrome. Fludrocortisone 0.1mg OD, follow-up 6 months. Fludrocortisone was successful in all 11 patients. No AE were reported.
Scott, 1995	RCT, N=58, children with neurally mediated syncope, 29 received fludrocortisone acetate (0.3 mg for 7 days, and then 0.1 mg/day) and 29 atenolol (25 to 50 mg, approximately 1 to 2 mg/ kg/day). Fludrocortisone or atenolol treatment was successful in 83% of patients, no difference was found between fludrocortisone and atenolol. AE fludrocortisone: 1 facial swelling, 1 bloating, 1 insomnia.
Hussein, 1996	N=64, elderly with OH, vasodepressor carotid sinus syncope, and/or vasodepressor neurocardiogenic syncope; fludrocortisone was administered in daily doses of 100 mg (72%), 50 mg (27%), and 200 mg (one patient). Thirteen patients died of unrelated causes, 33% discontinued fludrocortisone at a mean of five months. Reasons for discontinuing treatment were hypertension (5), cardiac failure (4), depression (3), oedema (3) and unspecified (2). In those who continued treatment BP did not differ significantly from baseline (follow up two to 21 months). Hypokalaemia developed in 24% at a mean of eight months;
Lieshout, 2000	Referred to, but content has not been discussed in the clinical overview.
Lieshout, 1993	N=8, neurogenic OH. Nocturnal head-up tilt plus fludrocortisone raised the BP in all 8 patients.
Alexrod, 2005	Retrospective study, N=341 of whom 175 patients received fludrocortisone. Treatment with fludrocortisone increased overall survival, improved mean blood pressure, and decreased pre-syncopal symptoms.
Schoffer, 2007	Randomised controlled crossover trial, N=17, Parkinson's disease. Thirteen patients received fludrocortisone or domperidone. Both treatments were successful. Six AE fludrocortisone: 2 nausea, 1 chest pain, 1 morning headache, light headedness and dizziness.
Sheldon, 2016	RCT, N=210. Fludrocortisone or placebo; marginally nonsignificant reduction in syncope in the fludrocortisone group (hazard ratio [HR]: 0.69: 95% confidence interval [CI]: 0.46 to 1.03; p = 0.069). Although the study did not demonstrate that fludrocortisone reduced the likelihood of vasovagal syncope by the specified risk reduction of 40%, significant effects were noted after dose stabilisation and in post hoc multivariable and on-treatment analyses.
Dacosta, 1993	No serious AE in the elderly.

The articles showed fludrocortisone has been successfully used for orthostatic hypotension as early as 1957. The MAH showed the well-established use of fludrocortisone for the treatment of orthostatic hypotension, but the available literature is limited. As this is considered a new indication for fludrocortisone, not authorised for the reference product, bridging data are needed to demonstrate that the new product is similar to the product(s) used in the supporting literature.

Bridging data

The MAH has selected the reference product Florinef due to its historic use and its presence in literature on the therapeutic treatment of orthostatic hypotension (as well as the other indications). Florinef is used in several referenced articles and additional references have been provided by the MAH. Bioequivalence has been demonstrated between Fludrocortisonacetaat Helm and Florinef. According to the Guideline on the investigation of bioequivalence, various immediate-release oral pharmaceutical forms can be considered to be one and the same pharmaceutical form, in this case tablets and an oral solution. No differences in bioavailability between these products are expected due to their fast and complete absorption. Overall, the MAH has reasonably addressed that the data as described in the literature could be bridged to the current product. This is considered acceptable.

IV.5 Clinical safety

The safety profile of fludrocortisone for the partial replacement treatment of Addison's disease and salt-losing adrenogenital syndrome is well-known. The main adverse events are due to the mineralocorticoid activity of fludrocortisone and include hypertension, oedema, cardiac enlargement, congestive heart failure, potassium loss, and hypokalaemic alkalosis. This is adequately reflected in the SmPC. The MAH summarised the available literature in which no additional safety concerns were raised for the treatment of orthostatic hypotension. This was acceptable.

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 Fludrocortisonacetaat Helm.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Florinef. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the new product is similar to the pharmacokinetic profile of the reference product. The use of fludrocortisone acetate as therapy in case of mineralocorticoid deficiency, adjunctive to glucocorticoid therapy, is shown to be well-established. For the indication of use in orthostatic hypotension, sufficient information is provided to support the indication and to bridge the new product to the products studied in literature. Clinical safety and risk management are adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with three participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Fludrocortisonacetaat Helm 0.1 mg/ml oral solution has a proven chemical-pharmaceutical quality and is a hybrid form of Florinef Acetaat, tablets 0.1 mg. Florinef Acetaat is a well-known medicinal product with an established favourable efficacy and safety profile. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The efficacy and safety of the new product are furthermore supported by literature.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fludrocortisonacetaat Helm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 December 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-

LITERATURE REFERENCES

Alexrod. (2005). Fludrocortisone in patients with familiar dysautonomia. *Clin Auton Res*, 284-291.

Armstrong. (1991). The effects of the somatostatin analogue, octreotide, on postural hypotension, before and after food ingestion, in primary autonomic failure. *Effect of octreotide on postural hypotension*, 135-140.

Balaji. (1994). Neurocardiogenic syncope in children with a normal heart. *JACC*, 779-785.

Bannister. (1969). An assessment of various methods of treatment of idiopathic . *Quarterly Journal of Medicine*, 377-395.

Cambell. (1975). 9-Alpha-Fluorohydrocortisone in the Treatment of Postural Hypotension in Diabetic Autonomic Neuropathy. *Diabetes*, 381-384.

Campbell. (1976). Therapeutic experience with fludrocortisone in diabetic postural hypotension. *British Medical Journal*, 872-874.

Chobanian. (1979). Mineralocorticoid-induced hypertension in patients with orthostatic hypotension. *The new England Journal of Medicine*, 68-73.

Dacosta. (1993). Benefits of fludrocortisone in the treatment of symptomatic vasodepressor carotid sinus syndrome. *Br Heart J*, 308-310.

Davis. (1987). The association of postural changes in systolic blood pressure and mortality in persons with hypertension: the Hypertension Detection and Follow-up Program experience. *Circulation*, 340-346.

Davidson. (1976). Diurnal Pattern of Water and Electrolyte Excretion and Body Weight in Idiopathic Orthostatic Hypotension. *Leeds*, 709-715.

Freeman. (2003). Treatment of Orthostatic Hypotension. *The Autonomic Nervous System*, 435-442.

Frick. (1966). 9-Alpha-fluorohydrocortisone in the Treatment of Postural Hypotension. *Acta Medica Scandinavica*, 293-299.

Harkel. (1992). Treatment of orthostatic hypotension with sleeping in the head-up tilt position, alone and in combination with fludrocortisone. *journal of Internal Medicine*, 139-145.

Hickler. (1959). Successful treatment of orthostatic hypotension with 9-alpha-fluorohydrocortisone. *The new England Journal of Medicine*, 788-791.

Hoehn. (1975). Levodopa-Induced Postural Hypotension. *Arch Neurol*, 50-51.

Hoeldtke. (1993). Treatment of orthostatic hypotension with erythropoietin. *The New England Journal of Medicine*, 611-615.

Hussein. (1996). Fludrocortisone in the treatment of hypotensive. *Heart*, 507-509.

Kupperman. (1955). Oral therapy of adrenal cortical hypofunction. *Oral therapy*, 1447-1449.

Lahrmann. (2006). EFNS guidelines on the diagnosis and management of orthostatic hypotension. *European Journal of Neurology*, 930-936.

Lieshout. (1993). Physical manoeuvres that reduce postural hypotension in autonomic failure. *Clinical Autonomic Research*, 57-65.

Lim S, Tan AH. Management of autonomic dysfunction in Parkinson's disease. 2017:93–110.

Lovas. (2008). Replacement therapy for Addison's disease: recent developments. *Endocrine & Metabolic*, 497-509.

Matsubara. (1990). Shy-Drager syndrome. Effect of fludrocortisone and L-threo-3,4-dihydroxyphenylserine on the blood pressure and regional cerebral blood flow.

Moya. (2009). Guidelines for the diagnosis and management of syncope (version 2009). *European Heart Journal*, 2631-2671.

Owen. (1957). 9-a-fluorohydrocortisone-induced hypertension in a male infant with adrenogenitalism, and in 6 adults with Addison's disease. *American Diabetes Association Fellow*, 272-279.

Schatz. (1963). Idiopathic Orthostatic Hypotension. *Diagnosis and Treatment*, 537-540.

Schatz. (1976). Corticosteroids in the Management of Orthostatic Hypotension. *Cardiology*, 280-289.

Schirger. (1962). Idiopathic Orthostatic Hypotension. *JAMA*, 822-826.

Schoffer. (2007). Efficacy of conservative treatment, fludrocortisone, and domperidone for symptomatic orthostatic hypotension in Parkinson's disease. *Abstracts / Journal of Clinical Neuroscience*, 1022-1023.

Scott. (1995). Randomized Comparison of Atenolol and Fludrocortisone Acetate in the Treatment of Pediatric Neurally Mediated Syncope. *THE AMERICAN JOURNAL OF CARDIOLOGY*, 400-402.

Sear. (1968). Orthostatic Hypotension. *Archives of Internal Medicine*, 467-471.

Sheldon. (2016). Fludrocortisone for the Prevention of Vasovagal Syncope. *JOURNAL OF T H E AMERICAN COL LE GE OF CARDIOLOGY*, 1-9.

Smith. (1984). Evidence that patients with Addison's disease are undertreated with fludrocortisone. *The Lancet*, 11-14.

Veazie. (2017). Fludrocortisone for orthostatic hypotension (Protocol). *Cochrane Library*.