COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Hydrocortison Tiofarma 1 mg, 2 mg, 5 mg, 10 mg and 20 mg, film-coated tablets (hydrocortisone)

NL/H/5804/001-005/MR

Date: 12 May 2026

This module reflects the scientific discussion for the approval of Hydrocortison Tiofarma 1 mg, 2 mg, 5 mg, 10 mg and 20 mg, film-coated tablets. The procedure was finalised on 31 August 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CAH	Congenital Adrenal Hyperplasia
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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MAA	Marketing Authorisation Application
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Hydrocortison Tiofarma 1 mg, 2 mg, 5 mg, 10 mg and 20 mg film-coated tablets, from Tiofarma B.V.

The product is indicated for: substitution therapy for

- Adrenocortical insufficiency in infants, children and adolescents (<18 years of age) and adults
- Congenital adrenal hyperplasia (CAH) in infants, children and adolescents (<18 years of age) and adults

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

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

Hydrocortison Tiofarma 20 mg ('Hydrocortison DMB 20 mg, tabletten') was authorised in NL with RVG 50730 since 15 July 1992 for the treatment of primary and secondary adrenal insufficiency (Addison crisis). The MAH submitted a new MAA for Hydrocortison 1, 2, 5, 10 and 20 mg based on well-established use, to add several lower strengths to the Hydrocortisone package: RVG 126831, RVG 126832, RVG 126833, RVG 126834, RVG 126835; registered in NL since 21 February 2022.

This mutual recognition procedure concerns a bibliographical application based on well-established medicinal use of hydrocortisone. For this type of application, the MAH needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Hydrocortisone immediate release tablets were first introduced into the European market at least ten years ago as a preoperative medication for substitutions therapy for adrenocortical insufficiency in infants, children and adolescents (<18 years of age) and adults, and congenital adrenal hyperplasia (CAH) in infants, children and adolescents (<18 years of age) and adults.

The MAH submitted a justification for bridging between their product and the product used in the literature for Hydrocortisone Hoechst tablets 10 mg and the Hydrocortone tablets 10 and 20 mg MSD (NL RVG 50730), based on comparable composition of the formulations.

The concerned member states (CMS) involved in this procedure were Belgium, Denmark, Finland, Germany, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Hydrocortison Tiofarma 1 mg is a round and biconvex ca. 3.5 mm and white or off-white film-coated tablet. Each tablet contains as active substance 1 mg of hydrocortisone.

Hydrocortison Tiofarma 2 mg is a round and biconvex ca. 4.5 mm and yellow film-coated tablet. Each tablet contains as active substance 2 mg of hydrocortisone.

Hydrocortison Tiofarma 5 mg is a round and biconvex ca. 7 mm and orange film-coated tablet. Each tablet contains as active substance 5 mg of hydrocortisone.

Hydrocortison Tiofarma 10 mg is a round and biconvex ca. 8 mm and red film-coated tablet. Each tablet contains as active substance 10 mg of hydrocortisone.

Hydrocortison Tiofarma 20 mg is a round and biconvex ca. 11 mm and brown film-coated tablet. Each tablet contains as active substance 20 mg of hydrocortisone.

The excipients are: lactose (monohydrate), povidone (E1201), sodium starch glycolate, magnesium stearate (E470b), partially hydrolysed polyvinyl alcohol (E1203), macrogol, talc (E553b), titanium dioxide (E171) (1 mg, 2 mg, 5 mg and 10 mg), quinoline yellow aluminium lake colourant (E104) (2 mg and 10 mg), sunset yellow aluminium lake colourant (E110) (5 mg only), Ponceau 4R (cochineal red A) colourant (E124) (10 mg only) and red and black iron oxide colourant (E172) (20 mg only).

The film-coated tablets are packed in white polyphenol (PP) bottles with white high-density polyethylene (HDPE) screw cap or polyvinyl chloride (PVC)/aluminium blister strips in a carton box.

II.2 Drug Substance

The active substance is hydrocortisone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water, sparingly soluble in acetone and in ethanol (96 %) and slightly soluble in methylene chloride. It contains several chiral carbons, hence, it can exhibit optical isomerism. Different polymorphic forms can exist, but only one is produced.

Two CEP procedures are 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 with the additional requirements indicated on the CEPs. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
The active substance is stable for 48 months respectively 36 months when stored under the stated conditions, depending on the manufacturer. Assessment thereof was part of granting one of 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.The choice and quantity of the excipients, and the manufacturing process are based on registered products. For the lower strengths, a biowaiver of strength is proposed. Sufficient comparative dissolution data have been provided.

Manufacturing process
Hydrocortison film-coated tablets are manufactured with a wet granulation method. This is a standard process which consists of blending, granulation, mixing, lubrication, compression and film-coating. A common powder blend is used for all strengths. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scale batches of the common blend and a bracketing approach is used for some of the strengths in accordance with the relevant European guidelines.

Control of excipients
The excipients are tested according to the corresponding Ph. Eur. The coating agents are tested according to in-house methods. 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, identity, mass, uniformity of dosage units, disintegration time, dissolution, assay, related substances and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from two production scale batches per strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for a variable number of batches for each strength in both packaging materials stored at 25°C/ 60% RH (24 months), 30°C/ 65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Small changes such as decrease of assay and dissolution, and increase of related substances (any other impurity and total impurities) have been observed; furthermore, for several batches of different strength and packaging, the content of unspecified impurities and an impurity raised above the limits under accelerated conditions. On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are 'Store below 25°C.'

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

Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of hydrocortisone 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, pharmacokinetics and toxicology data. This overview is considered adequate for this procedure and no further non-clinical studies are required.

III.2 Pharmacology

Because hydrocortisone has been developed about 70 years ago for replacement therapy in patients with adrenocortical insufficiency who would otherwise die, the historical development of the use of hydrocortisone in the treatment of adrenocortical insufficiency is

quite different from that of many other drugs used in medicine. This has consequences for the preclinical literature that is available.

Cortisol is secreted in a circadian and ultradian pattern. It activates the glucocorticoid receptor to exert its effects, which are very diverse. In several species (dogs, cats, horses and foals, ferrets, and pet birds) the use of hydrocortisone in the treatment of adrenocortical insufficiency has been described. Hydrocortisone can also be used for replacement therapy in critical illness-related corticosteroid insufficiency in animals. Physiological doses of hydrocortisone are required when hydrocortisone is used for the replacement treatment of patients with adrenocortical insufficiency.

Most secondary pharmacodynamic effects of hydrocortisone only occur when high pharmacological doses of hydrocortisone are administered. However, the effects on skeletal growth as well as growth retardation may occur at relatively low physiological doses. In addition, adverse cardiovascular effects of corticosteroids can be seen with relatively low physiological doses.

III.3 Pharmacokinetics

Hydrocortisone can be classified as a Class I compound according to the Biopharmaceutics Classification System (BCS), which means that it is easily absorbed. Metabolism is complex, and many intermediate metabolites have been identified. Hydrocortisone may be a substrate of P-glycoprotein, and is metabolised via CYP3A4. In animals, the ratio of hydrocortisone excreted via the faeces and urine varies greatly. In addition, substantial enterohepatic recirculation has been demonstrated, and several pharmacodynamic and -kinetic drug interactions have been described.

III.4 Toxicology

Relatively few toxicology data of hydrocortisone have been published. Hydrocortisone appears to be clastogenic in preclinical assays. However, no genotoxic potential has been observed in clinical practice. In addition, teratogenic effects of hydrocortisone were observed. Dosages at which these effects became apparent were very much higher than regular therapeutic dose levels. This observed teratogenicity of hydrocortisone in animals has not been confirmed in humans.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Hydrocortison Tiofarma is intended for substitution of extemporaneously prepared products in a limited patient population, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. 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, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Hydrocortisone is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, based on scientific literature. The overview justifies why there is no need to generate additional clinical data. This overview is considered adequate for this procedure and no further clinical studies are required.

IV.2 Pharmacokinetics

Hydrocortison Tiofarma is an oral, immediate release formulation, recommended for use in adults and children. Sufficient pharmacokinetic (PK) data have been provided to support the dose recommendation in adults and the paediatric population. Intake of food may delay absorption, resulting in lower maximum plasma concentration levels (C_{max}) and may even prolong clearance (Mah et al., 2004). In order to optimise the consistency of patient response to oral hydrocortisone therapy, the tablets should be taken without food (Webb & Krone, 2015). Hydrocortisone is an endogenous compound (originating from within the body), and is absorbed fast (the C_{max} is reached within 1 hour after intake). The absolute oral bioavailability of oral 20 mg tablets reported in literature is very high (96%) (Derendorf et al., 1991). It is a substrate of CYP3A4 and it is mainly metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol (Methlie et al., 2011). These are excreted in the urine, mainly conjugated as glucuronides, together with a very small proportion of unchanged hydrocortisone (Czock et al., 2005; Dollery, 1999; Schimmer & Funder, 2018). The elimination half-life is 1 to 2 hours (Toothaker et al., 1982). The exposure of hydrocortisone is less than dose proportional, probably because of the fast elimination (a great first-pass effect), but time dependency is unclear.

Bridging data

According to the Committee for Medicinal Products for Human Use (CHMP)'s Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), a BCS (Biopharmaceutics Classification System)-based biowaiver may represent a surrogate for *in vivo* studies. BCS-based class I biowaivers are applicable for an immediate release drug product if:

- the drug substance has been proven to exhibit high solubility and complete absorption (BCS-class I) and
- either very rapid (>85% within 15 min) or similarly rapid (85% within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements and
- excipients that might affect bioavailability are qualitatively and quantitatively the

same. In general, the use of the same excipients in similar amounts is preferred.

The MAH supported the bridging with solubility data, showing that hydrocortisone is a highly soluble drug according to the BCS classification. Moreover, literature data showed that hydrocortisone is absorbed for more than 85% (Charmandari et al., 2001; Derendorf et al., 1991). All strength tablets of Tiopharma showed over 85% dissolution within 15 minutes at the three pH levels and it was confirmed that the excipients of Hydrocortisone Tiofarma and of the hydrocortisone products described in literature could be considered not critical regarding absorption. It was sufficiently supported that hydrocortisone can be considered a BCS Class I drug and, therefore, bridging data may be covered by dissolution data.

The MAH submitted complete dissolution data for all the strengths tablets (1, 2, 5, 10 and 20 mg) versus the reference strengths mentioned in literature, at pH 1.2, 4.5 and 6.8, as described in the CHMP guideline. For a WEU application, bridging should be made to the specific products mentioned in literature, but for hydrocortisone, identifying information on the products is often lacking in the literature. This provided a challenge in bridging for Hydrocortisone Tiofarma. The MAH performed the dissolution studies with a number of formulations. The Hydrocortone 10 mg and 20 mg (UK) and Hydrocortison Hoechst 10 mg formulations were accepted by the Board as representative for bridging, as literature for these formulations indicated an uncomplicated absorption with an absolute bioavailability of about 96% (Charmandari et al., 2001). Secondly, Hydrocortison DMB 20 mg (NL RVG 50730) and the other products from DMB which are considered as standards in pharmacopoeia were added to the bridging strategy, as these products were likely used in the clinical studies on hydrocortisone published in literature. The data showed comparable dissolution between test and reference at the same tablet strengths (for Hydrocortone, depending on the batch used). Dissolution data have been provided for all formulations to support the bridging.

In conclusion, the bridge is sufficiently supported.

IV.3 Pharmacodynamics

In humans, cortisol is the main glucocorticoid (Brayfield, 2017; Dollery, 1999; Holt & Hanley, 2012; Oksnes et al., 2014; Schimmer & Funder, 2018). This stress hormone is produced by the cortex of the adrenal glands (Czock et al., 2005; Oksnes et al., 2014).

Cortisol production and secretion

The synthesis and secretion of cortisol is regulated by the hypothalamic–pituitary–adrenal axis (HPA-axis) (Arlt & Allolio, 2003; Carroll et al., 2018; Chan & Debono, 2010; Holt & Hanley, 2012; Lightman & Conway-Campbell, 2010; Martin-Grace et al., 2020; Oksnes et al., 2014; Oprea et al., 2019; Schimmer & Funder, 2018). The central pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) generates rhythmic signals which regulate the activity of the HPA-axis. In addition, acute stressors increase glucocorticoid production through activation of the HPA-axis at the level of the hypothalamus. The SCN pulsatility initiates corticotropic-releasing hormone (CRH) production in the neuroendocrine neurons of the hypothalamic paraventricular nuclei (Oprea et al., 2019). As a result, CRH induces the pituitary synthesis of adrenocorticotropic hormone (ACTH), which determines cortisol production in the adrenal

cortex. Finally, via a negative feedback loop, cortisol inhibits the HPA-axis. In the periphery and in target cells, cortisol and inactive cortisone are interconverted by isoforms (11β-HSD1 and 11β-HSD2) of 11β-hydroxysteroid dehydrogenase (11β-HSD) activity. Both CRH and ACTH are subject to negative feedback by cortisol, the levels of which are influenced in the periphery and in target cells by the balance of aforementioned 11β-HSD activity (Holt & Hanley, 2012).

Physiological function of cortisol

Glucocorticoids play a variety of roles in carbohydrate, protein, bone and calcium metabolism, salt and water homeostasis, anti-inflammatory and immunosuppressive effects, and effects of the central nervous system (Carroll et al., 2018; Oki & Yamane, 2007; Oprea et al., 2019; Stewart & Newell-Price, 2016).

Mechanism of action

Hydrocortisone is used in physiological doses for replacement therapy in adrenal insufficiency in an attempt to mimic as closely as possible the physiological circadian and ultradian excretion pattern of cortisol (Brayfield, 2017; Murray et al., 2017; Nussey, & Whitehead, 2001; Schimmer & Funder, 2018). Pharmacological doses of hydrocortisone are used when anti-inflammatory or immunosuppressive effects are required (Brayfield, 2017; Stewart & Newell-Price, 2016). These properties are used to suppress the clinical manifestations of disease in many disorders considered to have inflammatory or immunological components. For these purposes, the synthetic analogues are usually preferred, with their considerably reduced mineralocorticoid properties, linked with enhanced glucocorticoid properties.

IV.4 Clinical efficacy

The MAH proposed the following indications:
Hydrocortison Tiofarma is indicated as substitution therapy for:

- Adrenocortical insufficiency in infants, children and adolescents (<18 years of age) and adults
- Congenital adrenal hyperplasia (CAH) in infants, children and adolescents (<18 years of age) and adults

This indication is acceptable. This indication, with *ab explicit* mention of infants might highlight the fact that hydrocortisone cannot be swallowed by all children especially infants. Therefore, an advise was added to section 4.2 that other formulations of hydrocortisone are available for those children not able to swallow the tablets.

Primary adrenal insufficiency

The MAH provided a general summary with respect to Addison's disease, a particular cause of primary adrenal insufficiency, referred to the current clinical practice guideline of the Endocrine Society on primary adrenal insufficiency (Bornstein et al., 2016), which was composed by European and non-European authors, and discussed four publications in some more detail. Hydrocortisone has been in use for decades for treatment of primary adrenal insufficiency within the European Union. The clinical effects of hydrocortisone with respect to this condition are well-established. In the proposed SmPC, hydrocortisone at a dosage of 20 to 40 mg/day is recommended for adult patients with primary adrenal insufficiency. This dose range appears to be higher compared to recommended hydrocortisone of 15 to 25 mg/day in

two to three doses per day in the Endocrine Society Clinical Practice Guideline (Bornstein et al., 2016), and other publications (e.g. Husebye et al., 2014; Reznik et al., 2018). Therefore, and to bring the SmPC in line with the that of Efmody and to adhere to the guideline, the hydrocortisone dosing recommendations for adult patients with primary adrenal insufficiency were adjusted to 15 to 25 mg/day in two to three doses per day in the SmPC.

Secondary or tertiary adrenal insufficiency

The MAH provided a general summary with respect to secondary and tertiary adrenal insufficiency, referred to the current clinical practice guideline of the Endocrine Society on hormonal replacement in hypopituitarism in adults (Fleseriu et al., 2016), and discussed three publications in some more detail. It was proposed by the MAH to recommend a hydrocortisone dosage of 20 to 40 mg/day for adults with adrenal insufficiency in general, i.e. also for secondary and tertiary adrenal insufficiency. However, in submitted literature, a hydrocortisone dosage of 15 to 25 mg/day in two to three doses is recommended with respect to secondary and tertiary adrenal insufficiency (e.g. Grossman, 2010; Speiser et al., 2018). The hydrocortisone dosing recommendations for adult patients with secondary or tertiary adrenal insufficiency was therefore adjusted accordingly.

(Prevention of) trauma or disease in adult patients with known adrenal insufficiency or uncertain adrenal reserve

The MAH proposed to use the new product in case of trauma or disease in adult patients with adrenal insufficiency, in addition to or alternative for a treatment with medicinal products containing modified-release hydrocortisone. With respect to this, a distinction should be made between stable situations in which the hydrocortisone need is temporarily increased (e.g. increased exercise, surgery), and acute emergencies such as an adrenal crisis.

This prevention indication can be considered covered by the 'substitutions therapy' indication. Sufficient posology recommendations and warnings and precautions are provided to prevent adrenal crisis, therefore this indication is deleted.

Temporarily increased hydrocortisone need

A limited number of publications indicated that hydrocortisone dosing should be increased in particular situations such as strenuous activities (e.g. hiking), minor illness, or minor surgical procedures. A similar dosing recommendation was acceptable since there are no widely accepted hydrocortisone dosing recommendations in case of stressful situations in patients with adrenal insufficiency.

Treatment of adrenal insufficiency in paediatric patients

Regarding the clinical effects of hydrocortisone in paediatric patients with adrenal insufficiency, a submitted publication by Bowden et al. (2018), as well as external literature (e.g. Nofal et al. 2017, Nowotny et al. 2021, Husebye et al. 2021) support the use of hydrocortisone tablets in paediatric adrenal insufficiency. Guidance on the use of oral hydrocortisone treatment in paediatric patients with adrenal insufficiency is available in a Dutch database on medicinal products for paediatric patients (Kinderformularium). Recommended dosing for paediatric patients with primary, secondary, or tertiary adrenal insufficiency is 8 to 10 mg/m2/day. This dosing recommendation is supported by the

Endocrine Society Clinical Practice Guideline (which is 8 mg/m2/day in three or four divided doses) (Bornstein et al., 2016).

Substitution therapy in case of congenital adrenal hyperplasia in paediatric patients

Congenital adrenal hyperplasia is the most common form of primary adrenal insufficiency in paediatric patients (70% of patients). The disease characteristics of congenital adrenal hyperplasia differ from those of other forms of primary adrenal insufficiency e.g. with respect to the pathophysiology (genetic mutation versus genetic and other causes), the time of diagnosis (within the first weeks of life versus later in life), and virilisation that may occur in female patients (i.e. developing male characteristics), which is absent in other forms of primary adrenal insufficiency. These disease characteristics differ to such extent that congenital adrenal hyperplasia is often considered a separate disease entity, as in the SmPCs of Hydrocortisone Activase (DK/H/3174/001). This is therefore also acceptable for Hydrocortison Tiofarma.

The MAH submitted several publications on the pharmacokinetic, pharmacodynamic and clinical effects (growth, height, weight gain, signs of virilisation) of hydrocortisone with respect to paediatric patients with congenital adrenal hyperplasia. The clinical efficacy of hydrocortisone tablets for congenital adrenal hyperplasia in paediatric patients was initially unclear, but is supported by external literature (e.g. Merke et al., 2021, Bacila et al., 2021, Dabas et al., 2020). Hydrocortisone was the most frequently used glucocorticoid (87.6%) for the treatment of congenital adrenal hyperplasia in paediatric patients aged 0 to 18 years in the follow-up period from 1982 until 2018, in a publication by the European Society of Endocrinology (Bacila et al., 2021). This supports the clinical efficacy of hydrocortisone for the treatment of paediatric patients with congenital adrenal hyperplasia.

Proposed posology for paediatric patients with congenital adrenal hyperplasia is 10 to 15 mg/m2/day, usually divided over three doses a day. This posology is in line with the Endocrine Society Clinical Practice Guideline with respect to this condition (Speiser et al., 2018).

A single publication on hydrocortisone stress dosing in paediatric patients with congenital adrenal hyperplasia was submitted (El-Maouche et al., 2018). Parenteral hydrocortisone treatment instead of hydrocortisone tablets should be used for the treatment of an adrenal crisis in patients with congenital adrenal hyperplasia (Fleming et al. 2011; Chrisp et al. 2018; ;, 1995). Because of this, no use of hydrocortisone tablets for the emergency treatment of congenital adrenal hyperplasia should be recommended. Posology recommendations for severe and less severe situations are provided in the SmPC.

The hydrocortisone dosing recommendations for paediatric patients is 8-10 mg/m2/day for patients with adrenocortical insufficiency and 10-15 mg/m2/day for patients with CAH and the dosing frequency was adjusted to be usually distributed over three to four doses per day in the SmPC.

Conclusion

The indication and posology as proposed by the MAH are considered acceptable. The separate mentioning of infants allows a dosing advise for those not able to swallow the tablet.

Further, the substitution dose regimen for paediatric and adult patients was brought in line with the general recommendations (Endocrine Society) and the SmPC of Efmody (both dose and frequency).

IV.5 Clinical safety

The MAH provided an appropriate overview of the adverse events which were reported in adults in the literature. The risk of hypersensitive reactions to oral hydrocortisone treatment is low. Most important adverse events reported by the MAH have been included in the SmPCs of other hydrocortisone containing medicinal products. These adverse events have also been included in the current SmPC.

The MAH discussed adverse effects of hydrocortisone treatment which were reported in literature in paediatric patients with adrenal insufficiency and congenital adrenal hyperplasia. Respective adverse effects include hypertension, hyperglycemia, weight gain, osteoporosis, and gastric ulcers (Ucar et al., 2016). Hydrocortisone is more suitable than long-acting synthetic glucocorticoids (e.g., prednisone and prednisolone) regarding paediatric growth (Ucar et al., 2016). As excessive doses of hydrocortisone, especially during infancy, may cause persistent growth suppression, obesity and other Cushingoid features, complete adrenal suppression should be avoided (Clayton et al., 2002).

Adrenal crisis

During substitution treatment the most feared adverse event is the adrenal crisis (Addison crisis). Patients should be educated to recognise the events that might lead to an Addison crisis (psychological stress, planned surgery, illness and so on) and take some additional corticosteroids to avoid an adrenal crisis. This information has been included in the current SmPC.

Anaphylaxis

No publications on anaphylaxis and anaphylactoid reactions to oral hydrocortisone were retrieved. However, patients can develop hypersensitivity reactions to oral corticosteroids (Vatti et al,. 2014).

Though it is acknowledged that the risk of hypersensitive reactions to oral hydrocortisone treatment is low, this risk cannot be fully excluded based on submitted information and external literature (e.g. Kamm & Hagmeyer, 1999). Apart from this, immunosuppressive effects of glucocorticoid treatment have been reported (e.g. Butterfield et al., 1986; Stanbury & Graham, 1998). Hypersensitivity has been included in section 4.3 of the SmPC and anaphylactoid reactions were added to section 4.8.

Mortality

The mortality among patients with adrenal insufficiency was initially unclear. In response to questions, the MAH indicated that patients with primary adrenal insufficiency have a more than two-fold increased mortality ratio, mainly due to cardiovascular and infectious diseases according to submitted documentation (Bergthorsdottir et al. (2006), Bensing et al. (2008), Grossman (2010), Grossman et al. (2013), de Miguel Novoa et al. (2014), Johannsson et al. (2015)). In submitted publication by Hemmerstrand et al. (2017) the mortality in patients with

secondary adrenal insufficiency was dose-related. In patients with primary and secondary adrenal insufficiency, increased mortality has been reported in young patients, associated with infection and/or adrenal crisis.

In submitted documentation on the European Adrenal Insufficiency Registry (EU-AIR), the mortality for primary adrenal insufficiency was 1.0% and for secondary adrenal insufficiency was 1.5% during the period August 2012 until June 2017 (Quinckler et al., 2018). The main causes of death were cardiovascular disease (35%), infection (15%) and suicide (8%). Frequent adrenal crisis and a high mortality risk was reported in older, male patients with secondary adrenal insufficiency.

Laboratory abnormalities

The MAH reported in response to questions that various laboratory abnormalities may be observed upon corticosteroid treatment. Respective abnormalities include blood cells (e.g. increases in polymorphonuclear leucocytes and peripheral leukocytes, decreases in lymphocytes, monocytes and eosinophils) and changes in the fluid and electrolyte balance (e.g. hypokalaemia). The MAH noted that aforementioned abnormal laboratory results were obtained in patients without adrenal insufficiency. According to the MAH, the risk of such abnormalities are negligible when hydrocortisone is used in physiological doses to treat adrenal insufficiency. This position was substantiated by only one publication. Hence, the submitted body of scientific evidence was initially limited. In response, the MAH submitted publications by Olnes et al. (2016) and Nguyen et al. (2020) in which it was concluded that congenital adrenal hyperplasia patients and healthy control subjects exhibit significant differences in plasma metabolomes (such as cell count and electrolytes), which may be explained by glucocorticoid supplementation. In summary, haematological abnormalities and changes in the fluid and electrolyte balance may occur in patients treated with hydrocortisone. Changes in the plasma metabolome may occur upon glucocorticoid supplementation in patients with congenital adrenal hyperplasia. These abnormalities are addressed in the SmPC.

Dosing

The great challenge in the treatment of patients with adrenal insufficiency is to prevent both under- and overdosing. Because of this, it was included in proposed SmPC that the lowest dose of hydrocortisone and other corticosteroids should be used to control the condition under treatment. It was also indicated in the SmPC that if reduction in hydrocortisone dosage is possible, the reduction should be gradual.

Contra-indications

Systemic infection, or fungal infection in the absence of a specific treatment, and immunisation procedures during high doses of corticosteroids concern important contra-indications against the use of hydrocortisone tablets and were included in SmPC. However, only absolute contraindications are listed in section 4.3 of the SmPC and these are considered relative contraindications. Withholding patients with adrenal insufficiency or CAH from hydrocortisone treatment in case of systemic infection, fungal infections or immunisation could be life-threatening as they might develop adrenal crisis. Therefore, these contraindications have been deleted from section 4.3 of the SmPC.

Warnings and precautions

The MAH proposed relevant precautions and warnings in the SmPC. Some of these pertain to adrenal crisis, concomitant infections, mothers with pre-eclampsia and fluid retention, hypo- and hyperthyroidism, pheochromocytoma crisis, psychiatric adverse reactions, cirrhosis, and information cards. Though no dose adjustments are mandatory with respect to renal or hepatic impairment, caution is needed in patients with either or both of these conditions, due to decreased clearance of hydrocortisone in these patients. Careful dose titration of hydrocortisone tablets is needed in both paediatric and elderly patients.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (version 0.3 dated 5 August 2021), 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 Hydrocortison Tiofarma.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	N/A
Important potential risks	N/A
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 products in the literature. No new clinical studies were conducted. The final indications are widely used and known, and sufficiently discussed in the provided literature and therefore acceptable.

Risk management is adequately addressed. The clinical aspects of this product are approvable.

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 Dutch.
The test consisted of: a pilot test with five 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

Hydrocortison Tiofarma 1 mg, 2 mg, 5 mg, 10 mg and 20 mg have a proven chemical-pharmaceutical quality. Hydrocortison Tiofarma is an effective drug, which is considered widely established. The benefit/risk balance is considered positive. Bridging has been shown to be in compliance with the requirements of European guidance documents.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Hydrocortison Tiofarma with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 31 August 2023.

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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
NL/H/5804/001-005/IA/001/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph ○ Updated certificate from an already approved manufacturer	No	20-06-2024	Approved	N/A
	Change in pack size of the finished product • Change in the number of units (e.g. tablets, ampoules, etc.) in a pack ○ Change within the range of the currently approved pack sizes	Yes			
	Change in immediate packaging of the finished product • Change in type of container or addition of a new container ○ Deletion of an immediate packaging	Yes			

	container that does not lead to the complete deletion of a strength or pharmaceutical form				
NL/H/5804/001-005/IA/002/G	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) • All other Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)). Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph o Updated certificate from an already approved manufacturer	No Yes No	07-02-2025	Approved	N/A

NL/H/5804/001-005/IA/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC • Implementation of wording agreed by the competent authority	No	07-08-2025	Not approved	Invalid submission
NL/H/5804/001-005/IA/004/G	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC • Implementation of wording agreed by the competent authority	Yes	06-10-2025	Approved	N/A
NL/H/5804/001-005/IA/005/G	Change in the name and/or address of the marketing authorisation holder Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) • Manufacturer responsible for batch release	Yes Yes	27-11-2025	Approved	N/A