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 License RVG: 126831

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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 marketing authorisation was granted on 21 February 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

11β-HSD	11β-hydroxysteroid dehydrogenase
ACTH	Adrenocorticotropic hormone
ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
C_{max}	Maximum plasma concentration levels
CRH	Corticotropic-releasing hormone
DMB	De Magistrale Bereider
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
EU-AIR	European Adrenal Insufficiency Registry
FDA	Food and Drug Administration (of the United States of America)
HDPE	High density polyethylene
HPA-axis	Hypothalamic-pituitary-adrenal axis
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RVG	Register Verpakte Geneesmiddelen
SCN	Suprachiasmatic nucleus
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
WEU	Well-established use

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has 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:

- As substitution therapy in case of adrenal insufficiency in adults. The tablets will in this case be used in addition to or alternative for a treatment with medicinal treatment containing modified-release hydrocortisone;
- For prevention of adrenal crisis (Addison crisis) due to stress or exertion in case of adrenal insufficiency in adults. The tablets will in this case be used in addition to or alternative for a treatment with medicinal treatment containing modified-release hydrocortisone;
- As substitution therapy for adrenal insufficiency in paediatric patients and adolescents (<18 years);
- As substitution therapy for congenital adrenal hyperplasia in paediatric patients and adolescents (<18 years).

A comprehensive description of the indications and posology is given in the SmPC and the (proposed) indications are discussed in section IV.4 *Clinical efficacy* of this report.

The marketing authorisation has been granted via a national procedure under Article 10a of Directive 2001/83/EC (well-established use (WEU) application). Well-established medicinal use needs to be demonstrated for the active substance of the medicinal product for at least 10 years in the specific therapeutic area. In a WEU application, results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. Therefore, no clinical studies have been performed by the marked authorisation holder (MAH) and instead, bibliographical data are submitted.

Hydrocortisone as active substance in medicinal products has been in well-established medicinal use within the community for more than ten years, with recognised efficacy and an acceptable level of safety. Hydrocortisone was first approved by the FDA on 5 August 1952. In Europe, hydrocortisone was first registered as tablets in 1954, in Sweden. Hydrocortisone has been in clinical use extensively since about seventy years. Different formulations (e.g. (modified-release) tablets, granulate in capsules, scalp lotion, cream, ear and eye drops, injection fluid) have been authorised for marketing within The Netherlands for more than 10 years, for a wide variety of indications. Apart from authorised formulations, several ‘magistral’ hydrocortisone medicinal products in different strengths have been available for at least 10 years (e.g. 1 mg, 2 mg, 5 mg, 10 mg tablets).

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of 10 years, when this concerns a similar medicinal product with the same therapeutic indication. A similarity assessment has been performed between Hydrocortison Tiofarma and Plenadren (5 mg and 20 mg hydrocortisone modified release tablets), which obtained orphan market exclusivity on 14 November 2011, based on designation EU/3/06/372. The similarity assessment report was completed in September 2020, concluding the two products were partly similar and that Hydrocortison Tiofarma may only be used in case Plenadren treatment is not possible, or this treatment alone is insufficient. This was reflected in the indications and the procedure was therefore acceptable. The market exclusivity of Plenadren expired after November 2021.

II. QUALITY ASPECTS

II.1 Introduction

Hydrocortison Tiofarma are round, biconvex tablets that come in five strengths of hydrocortisone:

- 1 mg tablets, which are white or off-white,
- 2 mg tablets, which are yellow,
- 5 mg tablets, which are orange,
- 10 mg tablets, which are red,
- 20 mg tablets, which are brown.

The tablets are packed in PVC/Aluminium blisters or polypropylene tablet containers with a high density polyethylene (HDPE) cap.

The excipients are lactose monohydrate, povidone K30 (E1201), sodium starch glycolate (type A) and magnesium stearate (E470b), partly hydrolysed polyvinyl alcohol (PVA) (E1203), macrogol 3350 and talc (E553b).

Moreover, there are excipients specific to the strengths:

- 1 mg tablets contain titanium dioxide (E171),
- 2 mg tablets contain titanium dioxide (E171) and yellow quinoline (E104),
- 5 mg tablets contain titanium dioxide (E171) and sunset-yellow quinoline (E110),
- 10 mg tablets contain titanium dioxide (E171), yellow quinoline (E104) and Ponceau red quinoline (E124),
- 20 mg tablets contain red and black iron oxide colourant (E172).

II.2 Drug Substance

The active substance is hydrocortisone, an established active substance described in the European Pharmacopoeia (Ph.Eur.). According to the 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. Both active substance suppliers manufacture form 1, which is the only polymorph used in the manufacture of the drug product.

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 European Pharmacopoeia.

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 in line with the Ph. Eur. and with the additional requirements indicated on the CEP's. Batch analytical data from the drug product manufacturer have been provided, demonstrating compliance with the drug substance specifications.

The MAH provided nitrosamines risk evaluations from both active substance suppliers. Sufficient evidence has been provided that neither contaminated raw materials, contaminated starting materials nor contaminated intermediates are used in the manufacture of the active substance. Additionally, it was confirmed that cross-contamination has been evaluated and excluded.

Stability of drug substance

The active substance of manufacturer 1 is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM. Stability data support that the active substance of manufacturer 2 is stable for 36 months.

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

The manufacturing process has been validated according to relevant European and ICH guidelines. The 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 process has been properly described. Process validation data has been presented for three production batches of common blend and a bracketing approach is used for some of the strengths, meaning some results could be extrapolated.

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 product specifications include tests for appearance, identity, mass, uniformity of dosage units, disintegration time, dissolution, assay, related substances and microbial quality. The release and shelf-life specifications differ for the limit of total impurities and assay. Given the degradation of the active substance during storage, this is acceptable.

Analytical data have been provided for two production scale batches per strength demonstrating compliance with the release specification. The MAH submitted a risk assessment for the presence of elemental impurities into the drug product and the risk of nitrosamines in the manufacture of the final drug product. In conclusion, sufficient evidence has been provided that the risk for nitrosamines in the final drug product is negligible.

Stability of drug product

Stability data have been provided for a variable number of batches for each strength in both packaging materials (blisters or tablet containers), stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The stability studies are performed according to the ICH guideline. 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 impurities raised above the limits under accelerated conditions. Therefore, in line with ICH guideline Q1E, a shelf life of 27 months is acceptable, when the drug product is not stored above 25°C.

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

Certificates of suitability issued by the EDQM have been provided for lactose monohydrate, and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. The other substances are not of animal origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers 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

The nonclinical overview describes the preclinical pharmacology, pharmacokinetics and toxicology of hydrocortisone based on literature. This overview is considered adequate for this procedure.

III.1 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. Also in critical illness-related corticosteroid insufficiency in animals, hydrocortisone can be used for replacement therapy. 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.2 Pharmacokinetics

Hydrocortisone can be classified as a Class I compound according to the Biopharmaceutics Classification System (BCS), which means that it is easily absorbed. The metabolism concerning hydrocortisone 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 faces and urine varies greatly. In addition, substantial enterohepatic recirculation has been demonstrated (reuptake of a substance in the intestines, after it was excreted in the bile), and several pharmacodynamic and -kinetic drug interactions have been described.

III.3 Toxicology

Relatively few toxicology data of hydrocortisone have been published. Hydrocortisone appears to be clastogenic in preclinical assays, meaning it can cause mutations to chromosomes. However, no genotoxic potential has been observed in clinical practice. In addition, teratogenic effects (meaning it causes birth defects) of hydrocortisone were observed in animals. However, dosages at which these effects became apparent were much higher than regular therapeutic dose levels. This observed teratogenicity of hydrocortisone in animals has not been confirmed in humans.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Hydrocortisone 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.5 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 MEB finds 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, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB finds that 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 it 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

An overview of the assessment of proposed indications for Hydrocortison Tiofarma is provided in Table 1. More details of the assessments are discussed below.

Table 1 – The proposed indications which were approved (Yes) or rejected (No) based on the assessment of their legal base, indication and dosing recommendations

Abbreviation of proposed indication	Appropriate substantiation for well-established use legal base, for the proposed indication, and for the dosing recommendation?
Adrenal insufficiency in adult patients	Yes
Trauma or disease in patients with adrenal insufficiency	--
Temporarily increased hydrocortisone need	Yes
Emergency treatment	No
Adrenal insufficiency in paediatric patients	Yes
Congenital adrenal hyperplasia in paediatric patients	Yes

Emergency treatment in paediatric and adult patients	--
Severe bronchial asthma	No
Anaphylaxis	No
Drug hypersensitivity	No
Serum sickness	No
Angioneurotic oedema	No

Substitution therapy in case of adrenal insufficiency in adults

The MAH proposed to use the product in adult patients with adrenal insufficiency in addition to or as alternative for a treatment with medicinal products containing modified-release hydrocortisone.

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, 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.

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.

Emergency hydrocortisone treatment
The MAH indicated that parenteral (for example injection) hydrocortisone treatment is mandatory in case of acute trauma or disease in adult patients with known adrenal insufficiency or uncertain adrenal reserve (e.g. acute adrenal insufficiency, Addison crisis). Several publications on intravenous hydrocortisone treatment for critical illness-related corticosteroid insufficiency were submitted. It was acknowledged that intravenous hydrocortisone administration is needed in case of critical illness-related corticosteroid insufficiency. Submitted documentation on intravenous hydrocortisone administration is however not relevant for the currently proposed hydrocortisone tablets which are suitable for oral administration. This indication was not approved.

Treatment of adrenal insufficiency in paediatric patients
Initially, the MAH did not submit a discussion on the clinical effects of hydrocortisone in paediatric patients with adrenal insufficiency. However, a submitted publication by Bowden et al. (2018) in the second assessment round, 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/m^2/day. This dosing recommendation is supported by the Endocrine Society Clinical Practice Guideline (which is 8 mg/m^2/day) (Bornstein et al. 2016).

Substitution therapy in case of congenital adrenal hyperplasia in paediatric patients
Initially, it was unclear why hydrocortisone tablets were proposed separately in paediatric patients for treatment of primary adrenal insufficiency and also for the sub diagnosis congenital adrenal hyperplasia. The MAH acknowledged in response to questions that 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/m^2/day, usually divided over two to 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, Pearce 1995). Because of this, no use of hydrocortisone tablets for the emergency treatment of congenital adrenal hyperplasia should be recommended.

<u>Emergency treatment of severe bronchial asthma in adult and paediatric patients</u>
Recommendations in European treatment guidelines on emergency treatment of asthma as well as provided medical literature do not support the use of hydrocortisone tablets. Therefore, a positive benefit risk cannot be established. The indication emergency treatment of asthma was not acceptable.

<u>Emergency treatment of anaphylaxis, hypersensitivity reactions to medicinal products, serum sickness, and angioneurotic oedema in adult and paediatric patients</u>
Emergency treatment of anaphylaxis
The MAH did not substantiate the efficacy and dosing recommendations of oral hydrocortisone tablets in the treatment of anaphylaxis. This indication was not acceptable and was therefore dropped by the MAH.

Hypersensitivity reactions to medicinal products
The MAH referred to a publication on product information from the FDA to substantiate the clinical effects of hydrocortisone with respect to hypersensitivity reactions to medicinal products. No European literature was submitted. The MAH did not substantiate dosing recommendations for hydrocortisone tablets with respect to treatment of hypersensitivity

reactions to medicinal products. Hence, this part of the indication was not acceptable and was therefore dropped by the MAH.

Serum sickness
The MAH submitted several publications on the use of glucocorticoids for treatment of allergic conditions. The rational and dosing recommendations of hydrocortisone tablets with respect to treatment of serum sickness were however not discussed. This indication was not acceptable and was therefore dropped by the MAH.

Angioneurotic oedema
The MAH referred to a table in a textbook (Stewart & Newell-Price 2016) in which it is stated that corticosteroids can be used in the treatment of angioedema. However, the clinical effects and dosing recommendations for hydrocortisone tablets for treatment of angioneurotic oedema were not substantiated. Because of this, the indication angioneurotic oedema was not acceptable and was dropped by the MAH.

In conclusion, the approved indications are: substitution therapy in case of adrenal insufficiency in adults, prevention of adrenal crisis (Addison crisis) due to stress or exertion in case of adrenal insufficiency in adults, substitution therapy for adrenal insufficiency in paediatric patients and adolescents (<18 years) and substitution therapy for congenital adrenal hyperplasia in paediatric patients and adolescents (<18 years).

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 occurrence of adverse events in paediatric patients with adrenal insufficiency and congenital adrenal hyperplasia was initially unclear. In response to questions, the MAH discussed adverse effects of hydrocortisone treatment which were reported in paediatric patients in literature. Respective adverse effects include hypertension, hyperglycaemia, 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). Complete adrenal suppression should be avoided, as excessive doses of hydrocortisone, especially during infancy, may cause persistent growth suppression, obesity and other Cushingoid features (Clayton et al. 2002).

<u>Adrenal crisis</u>
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 (e.g. psychological stress, planned surgery, illness) and take some additional corticosteroids to avoid an adrenal crisis.

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).

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 twofold 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 a submitted publication by Hammerstrand 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 1.5% during the period of August 2012 until June 2017 (Quinkler 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 were 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 the 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 therefore included in the SmPC in the second assessment round.

Warnings and precautions
The MAH proposed relevant precautions and warnings in the SmPC. Some of these pertain to quiescent tuberculosis, mothers with pre-eclampsia and fluid retention, hypothyroidism, 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, 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 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB finds 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

The clinical benefit of hydrocortisone treatment by tablets is well-known and supported by the bibliographic data submitted in this procedure. The MAH discussed several studies to support the efficacy and safety of treatment with hydrocortisone tablets. No new clinical studies were conducted. The final indications are widely used and known, and sufficiently discussed in the provided literature and therefore acceptable.

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, film-coated tablets have a proven chemical-pharmaceutical quality.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Hydrocortison Tiofarma was authorised in the Netherlands on 21 February 2022.

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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
N/A	N/A	N/A	N/A	N/A	N/A