COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Acecort 3 mg, film-coated tablets (hydrocortisone)

NL License RVG: 127419

Date: 6 April 2022

This module reflects the scientific discussion for the approval of Acecort 3 mg, film-coated tablets. The marketing authorisation was granted on 27 October 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

ACTH	Adrenocorticotropic hormone
ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
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
CRH	Corticotropin-releasing hormone
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
HPA-axis	Hypothalamic-pituitary-adrenal axis
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph. Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TAMC	Total aerobic microbial count
TNFα	Tumour necrosis factor alpha
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total yeast/mould count

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 Acecort 3 mg, film-coated tablets, from ACE Pharmaceuticals B.V.

Acecort is indicated for the treatment of adrenal insufficiency in patients:
- who cannot be prescribed hydrocortisone containing modified release medication, or
- who require extra adrenal cortex hormone due to stress or extra exertion.

The product is an immediate release oral formulation.
A comprehensive description of the indications and posology is given in the SmPC.

Rationale

Hydrocortisone is the first choice of glucocorticoid replacement in patients with adrenal insufficiency (Quinkler et al., 2013; Simon et al., 2010; Sarafoglou et al., 2015). In general, during the treatment of adrenal insufficiency, it can be considered that the use of minor event-related dose increases is of more benefit than chronic overdose in substitution of cortisol. The extent of the needed dose increase is based on the available therapeutic guidelines and more importantly on the patient's individual needs which varies with differences in parameters such as weight, time of the day, lifestyle, stress level and the (ultra)circadian rhythm. Additional access to immediate release tablets allows a certain level of flexibility in dosing, limiting the risk of adrenal crisis in situations of expected mental or physical stress. This is also reflected in the current registered prescribing information for hydrocortisone as modified-release tablet (for maintenance therapy) referring to the recommendation to use immediate release hydrocortisone tablets in case of excessive physical and/or mental stress.

Legal base

The submitted dossier concerns a national application in the Netherlands, a line extension to the already approved products Acecort 1 mg (RVG 124716), 5 mg (RVG 124718), 10 mg (RVG 124719) and 10 and 5 mg (RVG 124838) film-coated tablets. These four products, from ACE Pharmaceuticals B.V., were authorised by the Netherlands through a mutual recognition procedure on 9 September 2021 (NL/H/5319/001-004/MR).

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, as hydrocortisone in adrenal insufficiency has well-established clinical use since about 60 years in the European Economic Area (EEA). For this type of application, applicants need to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least ten years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. The MAH also submitted data showing that the bioavailability of Acecort is similar to the bioavailability of the product most commonly studied in the scientific literature.

II. QUALITY ASPECTS

II.1 Introduction

Acecort is a pink, film-coated tablet, engraved with "HC 3". Each tablet contains as active substance 3 mg of hydrocortisone.

The tablets are packed in PVC-PE-PVdC/aluminium blister packs.

The excipients are:
Tablet core - lactose monohydrate, sodium starch glycolate and magnesium stearate
Tablet coating - polyvinyl alcohol (E1203), titanium dioxide (E171, macrogol 3350 (PEG, E1521), talc (E553b) and carmine (E120)

The excipients are well known and usual for this type of product.

II.2 Drug Substance

The active substance hydrocortisone is an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a white or almost white, crystalline powder and is practically insoluble in water, sparingly soluble in acetone and in ethanol (96%), and slightly soluble in methylene chloride. Hydrocortisone shows polymorphism.

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. Additional tests included on the CEP are particle size and residual solvents. A statement that the specifications for total aerobic microbial count (TAMC) and total yeast/mould count (TYMC) are met is provided.

Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines. The batches were stored below 25°C. Based on the data submitted, a retest period could be granted of five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
Acecort is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained.

Acecort tablets are developed as immediate release tablets. The amount of disintegrant is commonly used in immediate release formulation. It is sufficient to disintegrate the tablets within five minutes. The amount of lubricant is commonly used to prevent stickiness during tableting. As homogeneity, acceptance value, disintegration and dissolution profile proved to be well within specification for the process validation batches, no further process development was performed. Given the fact that the drug product concerns immediate release tablets and the manufacturing process is straight forward, this is acceptable.

Based on the dissolution data, similarity can be concluded between the 1 mg, 3 mg, 5 mg and 10 mg strength of Acecort tablets as all the tablets dissolved more than 85% within 15 minutes at pH 1.2, 4.5 and 6.8. Therefore, the efficacy and safety of Acecort 10 mg tablets can be extrapolated to the 3 mg strength.

Manufacturing process
The manufacturing process consists of mixing steps, direct compression of the tablet cores and coating of the tablets. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two pilot-scale batches and one production batch for Acecort 3 mg tablets, in accordance with relevant European guidelines. The provided validation data suffices. The process description and controls have been adequately described in the dossier.

Control of excipients
The excipients comply with the Ph. Eur. monographs, with additional functionality related characteristics if applicable. For the coating materials the quantitative composition have been provided. The specifications are acceptable.

Microbiological attributes

Acecort 3 mg film-coated tablets meet the requirements for microbiological quality described in the Ph. Eur., general chapter 5.1.4, *Microbiological quality of non-sterile pharmaceutical preparations and Substances for Pharmaceutical Use*.

Quality control of drug product

The finished products specifications are adequate to control the relevant parameters for the dosage form. The specifications includes tests for appearance, inscription, colour, dimensions, mass, disintegration, dissolution, water activity, identification, assay uniformity of dosage units, impurities and microbiological quality. The release and shelf life specifications are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data have been provided from three production scaled batches of the 3 mg product, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three batches in accordance with applicable European guidelines. The batches were stored at 25°C/60% RH (18 months), at 30°C/65% RH (12 months) and at 40°C/75% RH (six months). At intermediate conditions (12 months) out-of-specification results were observed for 'other impurities' after 12 months of storage in 1 batch. At accelerated conditions (six months) out-of-specification results were obtained for other impurities, total impurities, assay and uniformity of dosage units in all three batches. At long term conditions, no obvious trends were observed.
A forced degradation study was performed wherein the active substance and the crushed drug product were exposed to heat, acid and alkaline conditions. No photostability study was performed.

On basis of the data submitted, a shelf life was granted of 12 months for Acecort 3 mg film-coated tablets. The labelled storage conditions for all strengths are: "Store below 25°C. Store in the outer packaging in order to protect from light."

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate (bovine origin) and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. With respect to magnesium stearate, a clarification that it is manufactured with materials from vegetable origin is provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This well-established use application contains detailed references to published literature on non-clinical aspects. The information presented for the non-clinical pharmacology section was based on relevant scientific literature over the period of 1950 up to very recent. The submitted data is considered sufficient. Further, the MAH has submitted an environmental risk assessment to determine potential ecotoxicity of the active substance.

III.2 Pharmacology

III.2.1 Pharmacodynamics

III.2.1.1 Primary pharmacodynamics

Since hydrocortisone is a well-known active substance, the pharmacodynamic properties are well understood. Hydrocortisone is the synthetic form of the hormone cortisol. Cortisol is produced by the adrenal cortex and is a glucocorticoid belonging to the corticosteroids (ATC A01AC). Glucocorticoids, and thus also hydrocortisone, moderate a lot of responses in the body. In healthy situations cortisol formation and release is part of the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamic peptide corticotropin-releasing hormone (CRH) regulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. In turn ACTH stimulates the release of cortisol. Cortisol synthesised in the adrenal cortex enters the circulation, crosses the blood–brain barrier, and reaches the hypothalamus and anterior pituitary where it binds to a glucocorticoid receptor and inhibits the biosynthesis and secretion of CRH and ACTH.

The intended indication for hydrocortisone is the treatment of adrenal insufficiency for patients in whom treatment with modified release hydrocortisone alone is insufficient. In patients with adrenal insufficiency hydrocortisone replaces the otherwise biologically formed cortisol so that normal physiological actions can take place. Since hydrocortisone is the synthetic, exogenous, pharmaceutical form of the endogenous hormone cortisol, the pharmacological effects of hydrocortisone are the same as those of cortisol. Physiological cortisol is secreted in a pulsatile manner (Dorin et al., 2012), meaning that at different times of the day the concentration of cortisol in the plasma varies (Verma et al., 2010). In situations of stress or crisis the amount of hydrocortisone needed increases, the additional

hydrocortisone would mimic the naturally occurring increase. This is key for the body to be able to function normally. When hydrocortisone is administered it mimics cortisol, therefore it is involved in a number of physiological processes:

- Helps slow the immune systems inflammatory response;
- Helps balance the effects of insulin in breaking down sugar for energy;
- Helps maintain blood pressure and cardiovascular function; and
- Helps regulate the metabolism of proteins, carbohydrates, and fats.

Symptoms of adrenal insufficiency begin gradually. Patients begin to experience chronic, worsening fatigue, muscle weakness, loss of appetite, and as a result weight loss. Blood pressure decreases, causing dizziness or fainting when standing. It is common to experience skin changes and also mood changes. Hypoglycaemia also occurs, which is more severe in children than adults. Because of salt loss, craving salty foods is common. These symptoms progress slowly, therefore, they are ignored until a stressful event occurs, such as an illness or accident. This is known as Addisonian crisis (also called adrenal crisis) (Corrigan, 2018).

III.2.1.2 Secondary pharmacodynamics

At higher doses, hydrocortisone is used as an anti-inflammatory agent, and can be administered systemically or locally, depending on the indication.

Hydrocortisone induces the anti-inflammatory effect through influencing multiple signal transduction pathways. It switches off multiple activated inflammatory genes through inhibition of histone acetyltransferase and recruitment of histone deacetylase 2 activity in the gene transcriptional complex (Barnes, 2006). The actions through these receptors prevent the recruitment of leukocytes at the inflammation site, by inhibiting the display of adhesive molecules on the surface of the endothelium. Hydrocortisone also inhibits the ligand induced release of cytokines by endothelial and other inflammatory cells (Cornstein, 1992).

At the beginning of acute inflammation, an increase in hydrocortisone is important; however, prolonged elevation is not permitted by the body due to the danger of sepsis and inappropriately low immune responses towards infectious agents. Prolonged use of hydrocortisone leads to a reduced endogenous cortisol production, which in turn causes adrenal atrophy. This means that if the hydrocortisone is stopped, there will be no more ACTH stimulation. This coupled with reduced cortisol levels lead to problems with cardiovascular and glycaemic control.

III.2.1.3 Safety pharmacology

Data regarding non-clinical safety pharmacology is limited since hydrocortisone has been used for a long time in the clinical setting which has provided clinical insights. For a long time it was expected that the use of hydrocortisone in the treatment of adrenal insufficiency had no adverse effects since it was only used as a replacement for cortisol. More recently several studies have provided data that over-replacement with glucocorticoids in adrenal insufficiency can cause adverse effects (Mazziotti et al., 2017). The mechanisms for the effects seen at high doses are described here.

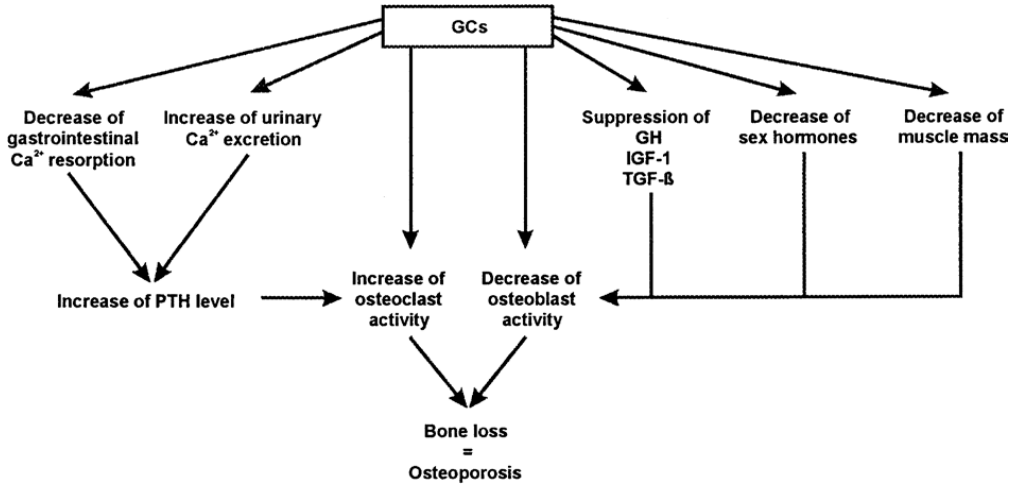
Cardiovascular system
Glucocorticoids are known to have cardiovascular effects. High doses of hydrocortisone can cause hypertension, salt and water retention and increased excretion of potassium. Underlying mechanisms are complex. Cardiovascular effects are expected to be caused by permissive activity on vasoactive agents, such as angiotensin II and catecholamines, and effects on mineralocorticoid receptors. At high hydrocortisone doses, the 11β-hydroxysteroid dehydrogenase type 2 isoenzyme, that converts hydrocortisone/cortisol in cortisone, gets saturated. As a result, hydrocortisone gets access to mineralocorticoid receptors in the kidney (Johannsson et al., 2015; Mazziotti et al., 2017).

Central nervous system
Existing psychiatric problems can be aggravated by glucocorticoid treatment but can also occur in previously stable persons. One of the most important mechanisms is expected to be the suppression of serotonin receptor (5-HT1A) expression by glucocorticoids through a glucocorticoid receptor-protein interaction (Schäcke et al., 2002).

Metabolism and endocrine system
Glucocorticoids are known to affect glucose metabolism. Excess of glucocorticoids causes both decreased insulin production as well as insulin resistance. As a result glucocorticoid therapy is associated with the risk of hyperglycaemia in patients without known diabetes mellitus (induction of diabetes) and worsened glycaemic control in diabetic patients (aggravation of diabetes) (Schäcke et al., 2002). Dyslipidaemia is also identified as an adverse effect of glucocorticoid treatment. The effects of glucocorticoids on lipid metabolism are complex and not fully elucidated. The effects include direct and indirect actions on lipolysis, free fatty acid production and turnover, very-low-density lipoproteins synthesis and fatty accumulation in liver. A positive correlation was found between plasma low-density lipoprotein (LDL) cholesterol and endogenous plasma cortisol in healthy men (Mazziotti et al., 2017)

Skeleton and muscle
Long-term treatment with glucocorticoids increases the risk for osteoporosis, which is associated with a high risk of bone fracture. Glucocorticoids affect bone metabolism via several pathways that are summarised in figure 1.

Figure 1. *Mechanism of glucocorticoid(GC)-induced bone loss (Schäcke et al., 2002)*



The loss of bone is complex and results from a number of additive effects. Glucocorticoids inhibit bone formation by suppressing osteoblast proliferation and activity. To maintain the serum Ca2+ level because of decreased gastrointestinal Ca2+ absorption and increased urinary Ca2+ excretion the release of parathyroid hormone is increased, leading to increased osteoclastic bone resorption. Glucocorticoids exert suppressive effects on growth hormone (GH), insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β). Reduced levels of adrenal sex hormones are also involved in the manifestation of osteoporosis. Glucocorticoids exert catabolic effects on skeletal muscle which also can contribute to the bone loss. The catabolic effects of glucocorticoids on skeletal muscles are mediated via several mechanisms. Glucocorticoids inhibit the glucose uptake in skeletal muscles that may contribute to the breakdown of muscle proteins. The muscle protein content is also directly affected by both stimulation of protein degradation and inhibition of protein synthesis (Schäcke et al., 2002).

Immune system

In pharmacological glucocorticoid treatment, the inhibition of the inflammatory and specific immune systems represents a central target. Consequently, adverse effects of glucocorticoid treatment include an increased risk for all kinds of infection. Moreover, due to the immunosuppression, a masking of infection symptoms may occur, preventing early clinical recognition (Schäcke et al., 2002).

Gastrointestinal system

Glucocorticoids can increase gastric acid secretion, reduce gastric mucus, cause gastrin and parietal cell hyperplasia and delay the healing of ulcers in animal studies. These effects are considered to be responsible for the gastrointestinal side effects such as peptic ulcers, upper gastrointestinal bleeding and pancreatitis (Schäcke et al., 2002).

Eye

After systemic administration adverse effects on the eyes have been demonstrated. These mainly include the development of cataract and glaucoma (Schäcke et al., 2002). Underlying

mechanisms involved in cataract development include increased glucose levels, caused by an increased gluconeogenesis rate; inhibition of Na+ /K+ -ATPase; increased cation permeability; inhibition of glucose-6-phosphate-dehydrogenase; inhibition of RNA synthesis; loss of ATP; and covalent binding of steroids to lens proteins. Glucocorticoids also form stable covalent adducts with the lysine residues of lens proteins in a non-enzymatic way which are only observed in steroid-induced cataracts (Schäcke et al., 2002).

Systemic glucocorticoid treatment is also associated with a high incidence of ocular hypertension. The main mechanisms leading to increased intraocular pressure during glucocorticoid treatment are morphological and functional changes in the trabecular meshwork cells, causing crucial alterations in extracellular matrix composition. (Schäcke et al., 2002).

Skin
Skin atrophy is the most frequent side effect of long-term topical corticosteroid therapy. An atrophogenic potential was also demonstrated for systemic glucocorticoid treatment. Glucocorticoids have suppressive effects on cutaneous cell proliferation and protein synthesis. They reduce the proliferative activity of keratinocytes and dermal fibroblasts and cause a decrease in protein synthesis by fibroblasts (Schäcke et al., 2002).

III.2.2 Pharmacokinetics

III.2.2.1 Absorption
Hydrocortisone is well absorbed following oral administration. In *in vivo* studies using male Sprague-Dawley rats, the oral absorption was 93% (Dowty and Dietsch, 1997). After intravenous administration in rats, half-life was found to be short (1.3 hours) and clearance was 2.38 L/h/kg. Volume of distribution at steady state was 1.24 L/kg (Mager et al., 2003).

III.2.2.2 Distribution
In an *in vivo* study using pregnant mice, hydrocortisone was mainly distributed to the maternal liver, bile, intestinal contents, kidney, urine and uterine luminal fluid (Waddell et al., 1972). Also in studies with pigs, highest concentrations were found in the liver (Bottoms et al., 1969). Hydrocortisone binds to albumin (56.2%) and presumably to corticosteroid-binding globulin. Hydrocortisone also binds to erythrocytes, but less tightly as to proteins (Florini et al., 1961). In animals as well as humans, it has been shown that placental transfer of hydrocortisone occurs with extensive conversion to cortisol and cortisone (Levitz et al., 1978; Beitins et al., 1973).

III.2.2.3 Metabolism
Hepatic cortisol metabolism is extremely variable amongst and in the species. Abel and colleagues investigated the cortisol metabolism in liver microsomes of mice, rats, hamsters, guinea-pigs and humans after incubation with 3H-hydrocortisone for two hours (Abel et al., 1992 and 1993). In rats, there are marked sex differences. In all species, hydrocortisone is converted to cortisol, but the specific cortisol metabolites that are formed differ in quantity and quality. In humans, guinea pigs, hamsters and mice, but not in rats, cortisone is observed (Abel et al., 1992; Abel at al., 1993).

III.2.2.4 Elimination

Data on the excretion of hydrocortisone are available from rats and guinea-pigs. In a study using rats, more than half of an intravenous, intramuscular, sublingual, or intragastrical dose of hydrocortisone was found to be excreted via faeces. The remainder is excreted via urine (Hyde et al., 1957). In a study by Wyngaarden et al. (1955), rats and guinea pigs were administered subcutaneously with hydrocortisone-4-C14. In the rat, 83 % of the dose appeared in bile in 3 hours, whereas only 66% was eventually excreted in faeces. The reabsorption and recirculation of the labelled biliary metabolites were demonstrated. In the guinea pig the rate of biliary excretion of labelled metabolites was considerably slower than in the rat, but 65% eventually entered the gut via this route. Most of these metabolites were subsequently reabsorbed and contributed to the 75% of the administered dose appearing in urine (Wyngaarden et al., 1955). Although small amounts of endogenous cortisol were found to be excreted in breast milk, this is not known for exogenous hydrocortisone (Kulski et al., 1981).

III.3 Toxicology

III.3.1 Single dose toxicity

Limited data are available about single-dose toxicity of hydrocortisone. Data are available from systemic administration in mice and rats. The approximate median lethal dose of hydrocortisone after intraperitoneal administration in adult albino rats was 150 mg/kg (Gupta et al., 1971). The median lethal doses of hydrocortisone following a single subcutaneous injection in mice were >8000, ≈8000 and 3073 mg/kg calculated respectively for a 7, 14 and 21 day observation period (Tonelli, 1966A). The values in rats were >1800, 591 and 449 mg/kg calculated for a 7, 14 and 21 day observation period, respectively (Tonelli, 1966B). Lethality following administration of single large doses of hydrocortisone was the result of secondary effects since deaths were delayed and some results can be attributed to the immunosuppressive effect of hydrocortisone.

III.3.2 Repeat-dose toxicity

Data on repeat-dose toxicity were only recovered from a summary report from the Committee for Medicinal Products for Veterinary Use (CVMP) (EMEA/MRL/377/98-FINAL). These studies were specifically designed to investigate hepatotoxicity. In rabbits receiving 15 or 25 mg hydrocortisone per animal, hepatic toxicity was observed by means of increased liver weight, focal hepatic necrosis and increased glycogen disposition. No observed effect level (NOEL) was established.

III.3.3 Genotoxicity

Although several positive results were published with regard to the mutagenicity of hydrocortisone (Bali et al., 1990), the reliability of these studies is questionable since there was no information of the purity of the material tested and the results are not confirmed by another report. Genotoxicity tests for hydrocortisone, performed according to GLP, provide no evidence for mutagenicity (Easotic scientific discussion, 2008).

III.3.4 Carcinogenicity

In a life-span study in rats the carcinogenic potential of hydrocortisone was investigated. Hydrocortisone administered orally in a dose of 37.5 mg/kg/week was found to have no carcinogenic effects (Schmähl et al., 1976).

III.3.5 Reproductive and developmental toxicity

Reproductive toxicity of hydrocortisone has been investigated in mice, rats and hamsters. As is known for other corticosteroids, hydrocortisone increases the incidence of cleft palates in mice and hamsters (Pinsky et al., 1965; Kalter et al., 1952; Rowland et al., 1983; Shah et al., 1976). In addition, it induced polycystic kidney disease in mice foetuses (Crocker et al 1991). In rats, hydrocortisone was shown to alter maternal metabolism, increase the number of resorptions, reduce placental size, reduce foetal size, and exert a detrimental effect on foetal viability (Gunberg et al., 1957). Since it is known that hydrocortisone can cross the human placenta to the foetus, these findings are likely relevant for humans.

III.3.6 Local tolerance

No studies on local tolerance after oral administration have been identified. Considering the route of administration, the used formulation and use of the compound for more than half a century in humans, this is considered acceptable for hydrocortisone.

III.4 Ecotoxicity/environmental risk assessment (ERA)

An ERA was submitted by the MAH. In the first phase an environmental risk estimation is made based on the drug substance, irrespective of its route of administration, pharmaceutical form, metabolism and excretion.

III.4.1 Screening for persistence, bioaccumulation and toxicity

Screening for persistence, bioaccumulation and toxicity according to the EU Technical Guidance Document (European Communities, 2003) is deemed unnecessarily, as the $\log_{Kow}$ for hydrocortisone is 1.6 (Pubchem).

III.4.2 Calculation of the Predicted Environmental Concentration (PEC)

The PEC in the surface water is estimated using the following formula:

$$PEC_{surfacewater} = \frac{Dose_{ai} * F_{pen}}{Wastew_{inhab} * Dilution}$$

$Dose_{ai}$= Maximum daily dose consumed per inhabitant, expressed in mg.inh-1.d-1
F_{pen} = Fraction of market penetration, based on published epidemiological data.
$Wastew_{inhab}$ = Amount of wastewater per inhabitant per day, default value of 200 L.inh-1.d-1
Diltution = Dilution factor, default value of 10
$PEC_{surfacewater}$ = Local surface water concentration, output in mg/L

Three review publications (Nicolaides, 2017; Charmandari, 2014; Arlt, 2003) provide an overview of the estimated prevalence of adrenal insufficiency. Secondary adrenal

insufficiency occurs more frequently than primary adrenal insufficiency. The estimated incidence of primary adrenal insufficiency in Europe has increased from 40-70 cases per million people in the 1960's to 4.4-6.0 new cases per million population per year more recently, with an estimated prevalence of 93-144 cases per million. Secondary adrenal insufficiency has an estimated prevalence of 150-280 per million, affecting more women than men. Age at diagnosis peaks in the sixth decade of life (Nicolaides, 2017; Arlt, 2003). Together a maximum prevalence of 424 per million can be calculated. F_{pen} is therefore 424/1000000*100= 0.0424%. The maximum dose per day used for the calculation is 30 mg (WHO).

$$PEC_{surfacewater} = (30\ mg * 0.0424) / (200\ L*inh^{-1}*d^{-1} * 10) = 0.000636\ \mu g/L$$

III.4.3 Conclusion

Hydrocortisone PEC surface water value is below the action limit of 0.01 µg/l and is not considered a PBT substance as log K_{ow} does not exceed 4.5. A phase II assessment was not necessary and hydrocortisone is not expected to pose a risk to the environment.

III.5 Discussion on the non-clinical aspects

This application refers to medicinal products where the active substance has a well-established medicinal use in the meaning of Commission Directive 2001/83/EC, with recognised efficacy and an acceptable level of safety. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided which is based on up-to-date and adequate scientific literature, with references from 1950 up to very recent. This overview justifies why there is no need to generate additional non-clinical data on pharmacology, pharmacokinetics and toxicology. Therefore, the MEB agreed that no further non-clinical studies are required.

Non-clinical toxicology studies have shown cleft palate and decreased bodyweight in off-spring, although not seen in human. The following statement is therefore added to Section 5.3 of the SmPC: "Reproductive toxicity studies with hydrocortisone have shown cleft palate and growth retardation in mice and rats. "

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 agrees that no further clinical studies are required.

For this bibliographic application, the MAH submitted bridging data to demonstrate that the 10 mg product applied for is similar to the 10 mg product described in literature. For that purpose the MAH requested a Biopharmaceutics Classification System (BCS)-based biowaiver for the 10 mg strength. Comparable bioavailability of the 10 mg tablet and the lower strength is subsequently demonstrated, as the 3 mg strength is not used in literature.

IV.2 Pharmacokinetics

IV.2.1 Scientific overview

IV.2.1.1 Absorption

The pharmacokinetics of single oral doses of 5, 10, 20 and 40 mg hydrocortisone suspension were published by Roger et al. (1982). The study was conducted in eight healthy male subjects whose endogenous hydrocortisone production was suppressed by dexamethasone administration. Absorption was rapid, the mean maximum plasma concentrations for hydrocortisone was achieved within 1 hour of dosing. Mean peak levels of hydrocortisone was 119 ng/mL following 5 mg dose and 175 ng/mL, 263 ng/mL and 389 ng/mL following 10, 20 and 40 mg dose respectively. The time of peak was independent of the dose.

In a pharmacokinetics study by Derendorf et al. (1991), 20 mg of hydrocortisone was studied following both intravenous and oral administration. The study was, like the study by Roger et al. (1982) conducted in eight healthy male subjects whose endogenous hydrocortisone production was suppressed by dexamethasone administration. Following oral administration the absolute oral bioavailability averaged 96% ± 20%, showing complete oral absorption. Absorption was rapid, achieving maximum hydrocortisone levels of 305 ng/mL after 1.2 hour (Derendorf et al., 1991).

IV.2.1.2 Distribution

Hydrocortisone is bound to plasma proteins such as corticoid-binding globulin and albumin; only the unbound portion is active. Binding with albumin happens with low affinity and high capacity protein fraction while binding with corticoid-binding globulin is through high affinity and low capacity protein fraction.

For hydrocortisone the ratio plasma/saliva is higher for low concentrations than for high concentration, likely due to non-linear protein binding of hydrocortisone. Volume of distribution after administration of 20 mg was 34 liter (Derendorf et al., 1991).

Thirteen different treatment regimens were observed, assessing pharmacokinetic parameters showing a volume distribution of 38.7 liter (with 39,7% intersubject variability) (Simon et al., 2010).

No publications of excretion of exogenous hydrocortisone into the breast milk has been identified. The concentration of endogenous cortisol in human milk samples obtained from women during the first 100 days after delivery ranged from 0.8 to 3.5 µg/dL and showed no systematic variation as a function of the postpartum day on which the sample was obtained (Rosner et al., 1976). Further, the concentration of milk glucocorticoids in humans seems to

be too low to have negative effects on the growth and development of breast-fed infants (Kulski and Hartmann, 1981).

Hydrocortisone/cortisol can cross the placental barrier, however, most cortisol crossing the placenta from maternal to foetal circulation is converted to cortisone. It's hypothesised that the conversion helps to protect the foetus from adverse effects such as growth retardation from maternal glucocorticoids (Yang et al., 1997; Murphy et al., 1974).

IV.2.1.3 Elimination

In 1982, Toothaker et al. studied the pharmacokinetics of single oral doses of 5, 10, 20 and 40 mg hydrocortisone suspension. The study was conducted in eight healthy male subjects whose endogenous hydrocortisone production was suppressed by dexamethasone administration. Drug elimination was found to be monophasic with a mean elimination half-life of 1.2 hours for the 5 mg dose and 1.7 hours for the 40 mg dose, showing that the elimination half-life was affected by the dose (Toothaker et al., 1982). As shown in the pharmacokinetics study by Derendorf et al. (1991), following intravenous administration, hydrocortisone was eliminated with a total body clearance of 18 liter per hour and a half-life of 1.7 hours, which is similar to the terminal half-life of 1.8 hours following oral administration (Derendorf et al., 1991).

A study by Buning et al. (2017), using subjects with secondary adrenal insufficiency, found that the clearance and volume of distribution were similar between two immediate release hydrocortisone doses for plasma free cortisol and salivary cortisol. The half-time was considered comparable between a lower and higher dose for the plasma free, plasma total and salivary cortisol levels. The maximum concentration for both the plasma total cortisol and plasma free cortisol was significantly higher for the higher dose compared to the lower dose, although this was only dose proportional for free cortisol levels and not for total cortisol levels (Buning et al., 2017).

The cortisol excretion in urine is found to be relatively low, as 80 to 90% of filtered cortisol is reabsorbed from the kidney. The conjugated metabolites, however, are filtered and excreted by the kidney with no reabsorption. More than 90% of secreted glucocorticoid is ultimately excreted in urine (McKay and Cidlowski, 2003; Peterson et al., 1955).

24-hour urine free cortisol closely relates to serum cortisol and shows minor variability between days and therefore might be a useful tool to assess hydrocortisone replacement therapy, although fluid intake, rates of 11-dehyrogenation, hepatic conjugation and conversion to other cortisol breakdown products may affect the 24-hour urine free cortisol levels. The influence of dose distribution in hydrocortisone replacement therapy in urine free cortisol excretion was investigated in 13 patients with hydrocortisolism with a total administered daily dose of 25 mg. The different dosing schedules existed of a) single dose of 25 mg at 8 am, b) 15 mg hydrocortisone at 8 am and 10 mg at 2 pm, c) 5 mg dose at 8 am, 10 am, 2 pm and 6 pm. The 24-hour urine free cortisol decreased significantly with increasing division of the total daily dose (Bliesener et al., 2003). A decreased level of urine free cortisol

suggests a lower risk of overexposure to cortisol when the total daily dose of 25 mg is divided in multiple doses over the day compared to one daily dose.

A cross-over randomised clinical trial described by Oksnes et al. (2014) compared 12-weeks continuous subcutaneous hydrocortisone infusion with thrice-daily oral hydrocortisone in patients with adrenal insufficiency. 24-hour excretion of cortisol and cortisone was significantly higher during subcutaneous administration than during treatment with oral hydrocortisone, whereas no differences were found in total cortisol metabolites (Oksnes et al., 2014).

IV.2.1.4 Metabolism

Cortisol is inactivated to cortisone by 11β-hydroxisteroid dehydrogenase, in the kidney but also colon, salivary glands and other target tissues (Arlt, 2003).

Corticosteroids metabolism occurs primarily in the liver where they are metabolised by enzymes resulting in a diminished physiologic activity and increased water solubility which facilitates excretion by the kidneys. Serum cortisol is mainly transformed to dihydrocortisol and then to tetrahydrocortisol, which is then conjugated to glucuronic acid. Around 10% of cortisol is converted to the 17-ketosteroid, which is then conjugated to sulfate which enhances urine excretion (McKay and Cidlowski, 2003; Peterson et al., 1955).

IV.2.1.5 Dose proportionality and time dependency

In the literature, the pharmacokinetics of hydrocortisone is dose-dependent, and the exposure is not dose proportional from 5 mg to 40 mg dose (Toothaker et al., 1982).

The MAH did not provide literature data regarding the time dependency. Time dependency is not considered critical because the dose of hydrocortisone needs to be adjusted individually and close drug monitoring is requested.

IV.2.1.6 Special populations

Impaired renal and hepatic function

Corticosteroid metabolism occurs primarily in the liver. Certain diseases of the liver result in elevated free hormone due to decreased corticosteroid metabolism, and a reduction in serum steroid-binding proteins (McKay and Cidlowski, 2003).

Hydrocortisone is metabolised by the liver, and inactivated and excreted by the kidneys. In case of severe hepatic or kidney impairment, the rate of metabolism, inactivation and excretion might be affected. As individual dose adjustment is applied to patients, specific dose adjustment for renal and hepatic impairment is not necessary.

Gender, race, weight, elderly

Based on literature studies (Mah et al., 2004; Johannsson et al., 2016), weight, height, body surface area and hydrocortisone dose affected hydrocortisone kinetics substantially, however, it was concluded that age and gender had no significant effect.

IV.2.1.7 Interactions

In vitro

A literature review for *in vitro* interaction has not been provided, which is also not necessary as *in vivo* interaction of hydrocortisone is already well-known.

In vivo

Medicinal products and food might affect the clearance of cortisol trough interaction with various enzymes responsible for the metabolism of hydrocortisone. Hydrocortisone is metabolised by cytochrome P450 enzyme CYP3A4, interactions with medicinal products that inhibit this enzyme will affect the hydrocortisone levels. CYP3A4 activity can be induced by drugs like rifampicin and several anticonvulsant agents resulting in an enhanced clearance of hydrocortisone and thus increased reduced systemic levels. Other products, such as azole antifungal agents and macrolide antibiotics, have an inhibiting effect on the clearance and, therefore, increase the terminal half-life (Buning et al., 2017; Husebye et al., 2015). Due to the interaction, there might be a need to adjust the hydrocortisone dose in case of co-administration of CY3A4 inhibiting products.

Generally, the administration of live or live-attenuated vaccines is contraindicated in patients receiving large (above 20 mg/day) or immunosuppressive doses of corticosteroids (Arvas, 2014). However, it is also acknowledged that immunisation may be undertaken in patients receiving corticosteroids as replacement therapy including adrenal insufficiency (KNMP, 2003). This seems to be likely as it is not used as add on therapy and, therefore, corticosteroid levels are close to natural occurring levels.

In patients with latent tuberculosis or tuberculin reactivity, the use of pharmacologic dosages of corticosteroids may cause a reactivation of the disease. Close monitoring for signs and symptoms of tuberculosis is recommended if corticosteroid therapy is administered to patients with a history of tuberculosis or tuberculin reactivity. During prolonged corticosteroid therapy, tuberculosis chemoprophylaxis may be considered (Cisneros and Murray, 1996).

IV.3 Bridging data of the products in the application with the products referred to in the literature

IV.3.1 BCS-based biowaiver

A BCS-based biowaiver has been requested for the 10 mg strength. The BCS is a scientific framework to classify drugs based on their aqueous solubility, permeability and dissolution. Drug substances can be classified in three classes according to the BCS:

- Class 1: high solubility – high permeability
- Class 2: low solubility – high permeability
- Class 3: high solubility – low permeability

The BCS-based biowaiver is applicable to Class 1 highly soluble drugs with known human absorption formulated as oral, immediate release formulations with the same pharmaceutical form as currently marketed hydrocortisone oral immediate release tablet

products. To fulfil the requirements for such a biowaiver, the MAH provided comprehensive documentation on solubility, permeability and dissolution of the product. The MAH was also required to show that the composition of Acecort and currently marketed hydrocortisone oral immediate release tablet products is similar. In addition, a supportive discussion was provided about the therapeutic index of the product. Hence, a BCS-based biowaiver is applicable only for drugs which are not considered to have a narrow therapeutic index.

In principle, the bridging data should be provided comparing Acecort with the literature formulation of hydrocortisone. However, the formulation of the hydrocortisone 10 mg tablets used in literature is unclear. Therefore in the current case, a comparison is provided with multiple currently marketed hydrocortisone oral immediate release tablet products, in order to justify Acecort formulation as similar as other hydrocortisone tablets. The MAH compared the dissolution of Acecort 10 mg tablets with Hydrocortisone Tiofarma 20 mg tablet (NL Licence RVG 50730), which is considered sufficient.

Solubility

High solubility is defined as the complete dissolution of the highest single dose administered as immediate-release formulation in 250 ml of buffers within the range of pH 1.0-6.8 at 37 ± 1°C (*Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr***). The highest single dose given is 20 mg of hydrocortisone, resulting in a concentration of 0.08 mg/ml. At least three buffers within the range of pH 1-6.8, usually set at pH 1.2, 4.5 and 6.8, should be investigated. In addition, a buffer at the pH similar to the pKa should be investigated, but only if this is within the range of pH 1-6.8. The reported pKa of hydrocortisone is 12.56 (Drugbank). It is not necessary to investigate the corresponding pH, because this value is higher than pH 6.8.

The solubility of hydrocortisone in water is reported to be 0.30 mg/mL at 25°C (Hagen and Flynn, 1983). Solubility data in aqueous buffer solutions at different pH and simulated gastric fluids can be found in literature (Pedersen et al., 2000). Solubility in aqueous buffer solutions was reported to be largely pH independent: pH 1.2 HCl-buffer: 0.37 mg/ml; pH 3.5 diluted acetic acid: 0.38 mg/ml; pH 6.5 phosphate-buffer: 0.35 mg/ml. This is expected regarding the high pKa value reported for hydrocortisone.

According to Pedersen et al. (2000), solubility of hydrocortisone in simulated human intestinal fluids is increased compared to aqueous buffer solutions. So solubility in aqueous buffer solutions is considered a worst-case approach.

Regarding the maximum dose of 20 mg of hydrocortisone, a minimum solubility of 0.35 mg/ml in aqueous buffer assures complete solution of the maximum dose in 250 ml of buffer in the complete range from pH 1.2 to pH 6.8. Therefore hydrocortisone in doses up to 20 mg is considered BCS Class I or BCS Class III, depending on the permeability.

In vitro dissolution
All tablet formulations are very rapidly dissolving and are therefore similar regarding *in vitro* dissolution. At pH 1.2, 4.5 and 6.8 all formulations dissolved more than 85% within 15 minutes.

Qualitative and quantitative composition
The composition of Acecort 10 mg tablets is simple without critical excipients, which is also similar with Hydrocortison Tiofarma.

Therapeutic index
Hydrocortisone is not considered a narrow therapeutic index drug.

Conclusion
Based on the available data hydrocortisone is a BCS Class 1 (high solubility and high permeability). The justification for BCS-based biowaiver for the Acecort 10 mg product is accepted.

IV.3.2 Biowaiver of strength

The efficacy and safety of Acecort 10 mg tablets can be extrapolated to the 3 mg Acecort strength since the general biowaiver criteria of the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) are met:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The formulations have similar qualitative and quantitative compositions. The excipients are widely used and not known to influence drug bioavailability.
- Appropriate *in vitro* dissolution data confirms the adequacy of waiving additional *in vivo* bioequivalence testing.

IV.4 Pharmacodynamics

IV.4.1 Mechanism of action

Hydrocortisone is naturally occurring as cortisol, a glucocorticoid. Cortisol binds and activates to glucocorticoid receptors, resulting in dissociation of heat shock proteins and subsequent dimerization. The receptor-ligand complex consequently trans-locates to the cell nucleus where it activates glucocorticoid response elements of the target genes, which enhances the transcription of glucocorticoid-regulated genes (transactivation). Suppression of transcription happens when the cortisol-bound glucocorticoid receptor interacts with transcription factors such as AP-1 or NF-κB. In this manner glucocorticoids can result in suppression of proinflammatory genes, key in the anti-inflammatory role of glucocorticoids.

Cortisol, like aldosterone, can bind to mineralocorticoid receptors, leading to transcription of epithelial sodium channels and serine/threonine-protein kinase which is involved in the regulation of e.g. a wide variety of ion-channels and cellular enzymes and contributes to regulation of e.g. renal natrium retention and insulin-dependent salt sensitivity of blood pressure. In healthy subjects cortisol levels increase when experiencing fever or infection.

This increase in cortisol diminishes the cytokine (such as interleukin-1 and tumour necrosis factor alpha (TNFα)) release and action preventing their potential toxic effects. In patients experiencing adrenal crisis the suppressive activity of increased glucocorticoid secretion is missing, leading to enhanced TNFα secretion, enhanced TNFα sensitivity and TNFα-induced glucocorticoid resistance (Figure 2) (Allolio, 2015).

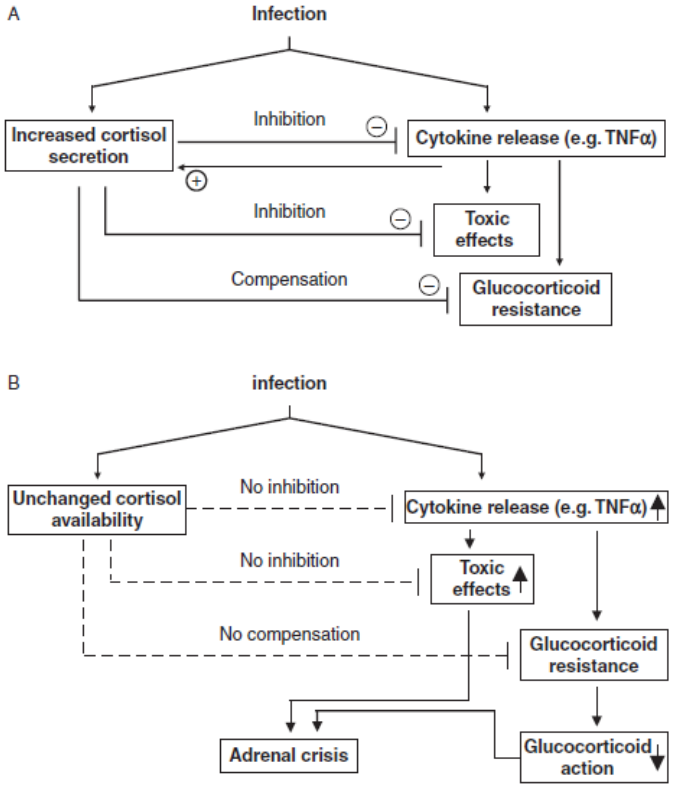


Figure 2. *Glucocorticoid and cytokine interaction during major infection in patients with intact adrenals (A) and patients with adrenal insufficiency on standard replacement therapy failing to adjust their hydrocortisone doses (B) (Allolio, 2015).*

It is expected that for surgeries the underlying mechanism might be the same as during surgery increased glucocorticoid secretion is missing which may lead to increased release of cytokines such as TNFα while for emotional stress may induce glucocorticoid resistance (Allolio, 2015).

IV.4.2 Primary pharmacology

The pharmacodynamic properties of hydrocortisone are well documented. Hydrocortisone is known to have a genomic and nongenomic effect. The genomic effect is mediated by hydrocortisone binding to glucocorticoid receptors leading to suppression or activation of gene transcription and consequently to activation or repression of protein syntheses. This can lead to different cellular effects such as anti-inflammatory/immunosuppressive effects (e.g. due to induction of certain anti-inflammatory cytokines or suppression of certain inflammatory enzymes), metabolic effects and suppression of osteocalcin. Nongenomic effect is normally more rapid than a genomic effect as this effect is independent of gene

transcription. Genomic effect can be divided in involvement of a receptor or without receptor (Czock et al., 2005). Nongenomic effects where receptors are not involved result from the mechanism that the glucocorticoids affect directly the cell membranes by physicochemical mechanisms.

IV.4.3 Secondary pharmacology

Endogenous cortisol has an extensive influence on different metabolism pathways and the functioning of organs. It regulates the stress response, contributes to the metabolism of glucose, regulates control of blood pressure and contributes to the immune system response.
High level of cortisol, such as in Cushing's syndrome, is often associated with impaired glucose tolerance, increased risk of osteoporosis, thinning of the skin, suppression of the immune response, increased blood pressure and in children growth impairment.

IV.4.4 Pharmacodynamic interactions with other medicinal products or substances

Potential interactions with other medicinal products are mostly related to the metabolism and excretion of hydrocortisone. Glucocorticoids may increase the clearance of aspirin, therefore salicylate levels should be monitored. Additionally, glucocorticoids may decrease the blood level of anticoagulants, monitoring of desired anticoagulant effect will therefore be needed. Glucocorticoid may decrease levels of insulin (Nicolaides et al., 2018).

Table 1. Interactions with other drugs

Drug	Effect	Potential action	Reference
Diuretics including potassium-depleting diuretics	Hypokalaemia	Monitor potassium levels	Nicolaides et al., 2018 Husebye et al., 2014
Mifepristone	Glucocorticoid receptor antagonist activity - reduced effect of corticosteroids	Monitor clinical response	Fleseriu et al., 2012

IV.4.5 Conclusion

Hydrocortisone is known to have a genomic and non-genomic effect. This can lead to different cellular effects such as anti-inflammatory/immunosuppressive effects (e.g. due to induction of certain anti-inflammatory cytokines or suppression of certain inflammatory enzymes), metabolic effects and suppression of osteocalcin.
Endogenous cortisol has an extensive influence on different metabolism pathways and the functioning of organs. It regulates the stress response, contributes to the metabolism of glucose, regulates control of blood pressure and contributes to the immune system response.

IV.5 Clinical efficacy

IV.5.1 Indication

The MAH decided to split the indication, and divided the original statement "Acecort has been developed for the treatment of adrenal insufficiency in patients in whom treatment with modified release hydrocortisone alone is insufficient" in the following indications:

- Supplementation of an increased demand caused by stress and/or illnesses in patients with hypocortisolism which are treated with sustained release hydrocortisone.
- When patients cannot be treated with a sustained release preparation.
- Treatment of children (only reflected in posology, not in SmPC section 4.1).

It is agreed with the MAH – and considered common knowledge – that in moments of stress patients with adrenal insufficiency are in need of an increased dose of corticosteroids to prevent a life-threatening Adison's crisis. The range of formulation provided by the MAH allows for a more controlled addition for a shorter period (as doubling the dose with a sustained release formulation might lead to over treatment with corticosteroids especially in short term stress moments). Apparently, the addition of hydrocortisone in stressful situations is not limited to patients on sustained hydrocortisone treatment. Therefore, this should be considered a separate part of the indication.

Although generally patients with adrenal insufficiency can be treated with a sustained release formulation, for a considerable portion of the patients the profile observed after sustained release formulations does not match the natural rhythm of the patient. Also patients with no stable daily rhythm are in need for a different hydrocortisone substitution. As this is to be considered on a case by case basis, no further detailing of this part of the indication is considered possible nor useful.

IV.5.2 Replacement therapy in patients with adrenal insufficiency

The Endocrine Society advices treatment of patients with hydrocortisone (15–25 mg/d) or cortisone acetate replacement (20–35 mg/d) applied in two to three daily doses in adults. In children, hydrocortisone (~8 mg/m^2/d) is recommended. In primary adrenal insufficiency once-daily fludrocortisone (median, 0.1 mg) should be added (Endocrine Society, 2016). Patients with adrenal insufficiency should be treated with hydrocortisone (or cortisone acetate if hydrocortisone is not available), which is the most physiological option for glucocorticoid replacement. The recommended daily hydrocortisone dose is 10–12 mg/m^2; it can be given in two to three doses, with administration of half to two thirds of the total daily dose in the morning. Longer-acting synthetic glucocorticoids, such as prednisolone, prednisone, and dexamethasone, should be avoided.

In the guidance of Euadrenal (European Expert Consensus meeting) is stated Glucocorticoids are secreted into the systemic circulation in a pulsatile (ultradian) and circadian fashion, with a peak in the morning and reaching a nadir at midnight. Individuals with normal adrenal

function produce between 5 and 10 mg of cortisol per m^2 of body surface area per day, equivalent to an oral replacement dose of 15–25 mg per day of HC.

Currently, there is a significant heterogeneity in the type, dose, frequency and timing of glucocorticoid replacement in real-world clinical practice. This reflects dose individualisation based on patient symptoms and lifestyle in the absence of data supporting the optimal regimen (Murray et al, 2017).

IV.5.3 Hydrocortisone in prevention and treatment of acute adrenal crisis (Addison's crisis)

In the guidance of Euadrenal (European Expert Consensus meeting) is stated that an acute adrenal crisis is a life-threatening emergency that requires immediate diagnosis and treatment. Even a mild upset stomach may be a precipitating event as patients do not absorb their medication when they need the medication more than ever. Prompt recognition and therapy is vital for the patient, but unfortunately this is not always the case. The frequency of acute adrenal crises among patients with PAI is 6-8 per 100 patient-years, and precipitating events are often vomiting and/or diarrhoea, infections, surgical procedures, injuries, myocardial infarction, severe allergic reactions, severe hypoglycaemia in diabetic patients and treatment failures in poorly educated or noncompliant patients. Rapid intravenous administration of HC (100 mg) is important.

To prevent the occurrence of adrenal crisis it is of importance to timely acknowledge (upcoming) stress events, both physical stress such as illnesses but also psychological stress such as a conducting an exam or interview. As also recommended in several publications, patients should receive appropriate education to manage their daily medications and understand the need for necessary dose adjustment in context of minor to moderate stress (Husebey et al., 2014; Bornstein et al., 2016; Johannsson et al., 2014; AdrenalNet, 2018).

The range of formulation provided by the MAH allows for a more controlled addition for a shorter period (as doubling the dose with a sustained release formulation might lead to overtreatment with corticosteroids especially in short term stress moments). Apparently, the addition of hydrocortisone in stressful situations is not limited to patients on sustained hydrocortisone treatment. Therefore this part of the indication is deleted in the indication.

IV.5.4 Hydrocortisone substitution in children

There is clearly a need for treatment children with adrenal insufficiency. Currently available immediate release hydrocortisone or Alkindi are possible treatment options for children. Children require much smaller doses (of the order of 1–2 mg three times daily in infants or 8-12 mg/m2/ day divided over 3 dosages in ratio 2:1:1) (Kinderformularium, 2019). Thus, there is a need for low strength hydrocortisone formulations for this paediatric patient group (Kauzor et al., 2014; Porter et al., 2017). The drawbacks of a sustained release formulation as mentioned for adults are also observed with children. Further, the controlled release formulation does not allow the flexibility necessary for an optimal replacement in children. Therefore, the immediate release preparation of Acecort and the range of strengths is considered an useful treatment option for children.

Although Alkindi has marketing protection based on a PUMA procedure, there is room for the paediatric indication with the span of formulations applied for, provided that such an indication would be supported by data not protected under the data exclusivity for Alkindi. The submitted literature was not based on the use of Alkindi and therefore acceptable. Based on the literature and the current guidelines (ESPE and ASPEN), there is room for the use of an immediate release hydrocortisone formulation. However, for the patients who cannot swallow tablets an alternative treatment options should be considered.

IV.6 Clinical safety

Hydrocortisone is given as replacement therapy aimed at restoring normal cortisol levels. The adverse reaction profile in the treatment of adrenal insufficiency is therefore not comparable to that in other conditions requiring much higher doses of oral or parenteral glucocorticoids. The current product has been developed for the treatment of adrenal insufficiency in patients in whom treatment with modified release hydrocortisone is insufficient.

The main concern with hydrocortisone treatment is over- and underdosing, with more recent publications considering the need to ensure the lowest possible dose of hydrocortisone to avoid chronic overdosing while allowing daily flexible dosing where needed such as in case of physical or mental stress to avoid adrenal crisis. The safety concerns of hydrocortisone in patients with adrenal insufficiency are limited as also expressed in the SmPC for Alkindi and Plenadren for which controlled studies have been conducted. Also, review of the SmPC for hydrocortisone Tiofarma (NL Licence RVG 50730) indicates that hydrocortisone does have very limited undesirable effects when dosing of substitution is correctly done.

The current application is based on review of the scientific literature. For this reason the side effects listed in the SmPC are all of unknown frequency and include:

- Nervous system disorders
  - Vertigo
  - Headache
- Gastrointestinal disorders
  - Gastroenteritis e.g. including diarrhea and nausea
- Muscoskeletal and connective tissue disorders
  - Arthralgia
- General disorders and administration site conditions
  - Fatigue

IV.7 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 Acecort.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• Acute psychiatric effects • Glucocorticoid under-and overreplacement due to drug-drug interactions • Using too low a dose of hydrocortisone (glucocorticoid under-replacement) • Using too high a dose of hydrocortisone (glucocorticoid over-replacement) • Abnormal stomach emptying (gastrointestinal emptying or motility disease or disorder, including pharmacological therapies affecting gastrointestinal emptying or motility)
Missing information	• None

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

IV.8 Discussion on the clinical aspects

For this well-established use application, reference was made to clinical studies and experience with the active substance hydrocortisone. No new clinical studies were conducted. The MAH presented an adequate literature overview of hydrocortisone pharmacokinetics, pharmacodynamics, clinical efficacy and clinical safety. The beneficial effect of hydrocortisone as replacement therapy aimed at restoring normal cortisol levels is considered established. The adverse reaction profile in the treatment of adrenal insufficiency is not comparable to that in other conditions requiring much higher doses of oral or parenteral glucocorticoids.

A BCS-based biowaiver has been granted for the 10 mg strength, and a biowaiver of strength for the 3 mg product. Hydrocortisone given as 3 mg tablets give the possibility to correct for the subtle changes seen in the normal physiology and can be considered an addition to the current treatment options.

Risk management is adequately addressed. The current application is based on review of the scientific literature. For this reason, the side effects listed in the SmPC are all of unknown frequency and include: vertigo, headache, gastroenteritis e.g. including diarrhoea and nausea, arthralgia and fatigue.

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 four 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

Acecort 3 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Acecort is an effective immediate release drug product for the treatment of adrenal insufficiency, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that well-established use has been demonstrated for Acecort, and have therefore granted a marketing authorisation. Acecort was authorised in the Netherlands on 9 September 2021.

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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