SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Acecort and associated names (see Annex I)> 1 mg film-coated tablets
<Acecort and associated names (see Annex I)> 5 mg film-coated tablets
<Acecort and associated names (see Annex I)> 10 mg film-coated tablets
<Acecort and associated names (see Annex I)> 10 and 5 mg film-coated tablets
[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Acecort> 1 mg film-coated tablets contain 1 mg hydrocortisone
<Acecort> 5 mg film-coated tablets contain 5 mg hydrocortisone
<Acecort> 10 mg film-coated tablets contain 10 mg hydrocortisone

Excipient(s) with known effect
<Acecort> contains lactose, sunset yellow FCF (E110, <Acecort> 5 and 10 mg), ponceau 4R (E124, <Acecort> 5 mg) and allura red (E129, <Acecort> 10 mg).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The film-coated tablets are round and have a diameter of 8 millimeters.

<Acecort> 1 mg film-coated tablets are white and engraved with HC 1
<Acecort> 5 mg film-coated tablets are orange and engraved with HC 5
<Acecort> 10 mg film-coated tablets are red and engraved with HC 10

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<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

4.2 Posology and method of administration

Posology

Adults
When hydrocortisone containing modified release medicines cannot be prescribed
The usual dose varies between 15 mg and 25 mg of hydrocortisone per day. This dose should be taken three times (morning, early afternoon and early evening). The morning dose is generally 2 times higher than the afternoon and evening dose.

The correct dosing schedule should be individually titrated for each patient, based on laboratory values and the patient's wellbeing.

In case of stress
In situations where the patient is exposed to excessive physical and/or mental stress while on maintenance therapy, additional doses of <Acecort> can be taken.

The additional doses of <Acecort> should be taken in the afternoon/evening, when hydrocortisone levels in the body are decreased. The degree of stress determines the additional hydrocortisone dose, which can vary from 2 mg to 20 mg, or doubling the usual daily dose of hydrocortisone. Patients and their caregivers should be informed of the necessary dose adjustments in case of stress. In addition, patients and their caregivers should pay close attention to the symptoms of acute adrenal insufficiency that may develop.

In case of temporary dose increase in periods of stress, return to the previous dose should be done as soon as the acute period has passed.

Paediatric population
For children and adolescents, recommended replacement doses of hydrocortisone are 8-10 mg/m^2/day for patients with adrenal insufficiency alone and 10-15 mg/m^2/day in patients with congenital adrenal hyperplasia, typically in three divided doses, whereby the first dose is twice as high as the second and third dose. In case of stress or increased exertion, the dose should be increased 3 to 5 times.

Method of administration
The film-coated tablets can be taken with or without food.

Renal and hepatic impairment
For patients with adrenal insufficiency it is recommended to monitor the clinical response.

Paediatric population
This product is suitable for use in children. Children who cannot swallow the film-coated tablets should be treated with a more appropriate dosage form.

Elderly
In case of age related low body weight, it is recommended that the clinical response is monitored and that the dose is adjusted appropriately. A dose decrease may be required.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Close monitoring of the patient, including weight, blood pressure and electrolyte level, is necessary during hydrocortisone treatment.

Most undesirable effects of corticosteroids are dose and duration of exposure related. Therefore, undesirable effects are less likely when using corticosteroids as replacement therapy. In all patients suffering from adverse events under- and/or overdosing should be considered, and prescribers are encouraged to investigate the cause of the undesirable effects and increase or decrease the dose.

Acute adrenal insufficiency
In patients with adrenal insufficiency, acute adrenal insufficiency and adrenal crises may develop despite taking hydrocortisone. Patients should therefore be made aware of the signs and symptoms of acute adrenal insufficiency and adrenal crisis and seek medical attention immediately. In adrenal crisis, parenteral, preferably intravenous administration of hydrocortisone (in high doses) with sodium chloride solution for infusion (9 mg/ml, 0.9%) should be used according to current treatment guidelines.

Patients who experience vomiting or diarrhoea may not absorb enough oral hydrocortisone. In these situations parenteral hydrocortisone should be administered.

Psychiatric effects
Psychiatric adverse reactions may occur with systemic glucocorticoids. This may occur during setting of treatment and during dose adjustments. Risks may be higher when high doses are given. Most reactions resolve after dose reduction, although specific treatment may be necessary.

Infections and immunisation
Substitution therapy of corticosteroids for people with adrenal insufficiency do not cause immunosuppression and is therefore not a contraindication for administration of live vaccines.

Infection should not be more likely at a replacement dose of hydrocortisone, but all infections should be treated seriously and stress dosing of steroids initiated early (see section 4.2). Patients with adrenal insufficiency are at risk of life-threatening adrenal crisis during infection so clinical suspicion of infection should be high and specialist advice should be sought early.

When higher than physiological doses are administered for a certain time, monitoring for the occurrence of any infectious complications (due to bacteria, such as Mycobacteria or yeasts) should be done and vaccinations should be avoided.

Higher than physiological doses of hydrocortisone
High (supraphysiological) doses of hydrocortisone can cause an increase in blood pressure, salt and water retention and an increased excretion of potassium. Long term treatment with higher than physiological doses of hydrocortisone, may lead to clinical features similar to those of Cushing's syndrome (increased adiposity, abdominal obesity, hypertension and diabetes). Such long term treatment can lead to an increased risk of cardiovascular morbidity and mortality.

Higher doses of glucocorticoid substitution can potentially lead to decreased bone mineral density.

Extra caution should be taken in patients who appear to be predisposed to getting complications due to:

- a history of gastrointestinal ulcer disease
- latent tuberculosis (recent Mantoux rash)
- severe osteoporosis
- severe hypertension
- diabetes mellitus
- corticosteroid induced psychosis
- increased gastrointestinal motility
- heart failure
- a history or family member with a history of glaucoma

Glucocorticosteroids may increase insulin resistance, therefore the clinical manifestations of patients with diabetes mellitus should be monitored. Patients with subclinical diabetes mellitus can develop clinical diabetes mellitus.

Visual disturbances
Visual disturbances may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy which have been reported after use of corticosteroids.

Hypertrophic cardiomyopathy
Hypertrophic cardiomyopathy was reported after administration of hydrocortisone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

Lactose intolerance
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorptions should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of CYP3A4 inducers or inhibitors
The use of CYP3A4 inducers or inhibitors may increase or decrease the systemic effect of the corticosteroids. The dose of hydrocortisone may need to be increased or decreased when taking CYP3A4 inducers (such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and efavirenz) or inhibitors (such as ketoconazole and erythromycin).

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Other interactions
The effect of corticosteroids may be reduced after treatment with mifepristone.

The use of glucocorticoids together with diuretics, and specifically potassium-depleting diuretics may cause hypokalaemia. Patients should be monitored for hypokalaemia.

Glucocorticoids may increase the clearance of acetylsalicylic acid, salicylate levels should be monitored.

Glucocorticoids may decrease the blood level of anticoagulants, monitoring of desired anticoagulant effect will therefore be needed.

Glucocorticoids may weaken the effect of antidiabetics (including insulin), and a dose increase may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy
Corticosteroids can reach the foetus through the placenta. In humans, there is no clear evidence of teratogenic effects to date, as observed in animal studies (see section 5.3). There is no evidence that hydrocortisone replacement therapy in pregnant women with adrenal insufficiency is associated with adverse effects on the mother and/or foetus. <Acecort> can be used as replacement therapy during pregnancy. Guidance of an endocrinologist during pregnancy is recommended.

Breast-feeding
Small amounts of corticosteroids are excreted in breast milk. No adverse effects on the nursing infant are expected during hydrocortisone replacement therapy. Hydrocortisone replacement therapy can be used during breastfeeding.

Fertility
Patients with adrenal insufficiency have been shown to have a reduced ability to carry a child to full gestation, which is most likely due to the underlying disease. There is no evidence that hydrocortisone replacement therapy will affect fertility.

4.7 Effects on ability to drive and use machines

Hydrocortisone has a minor influence on the ability to drive and use machinery. Fatigue and dizziness have been reported. Untreated and poorly treated adrenal insufficiency can affect the ability to drive and use machinery.

4.8 Undesirable effects

Summary of the safety profile
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. Undesirable effects in adrenal insufficiency patients treated with physiological levels of hydrocortisone are mainly related to over- or under-dosing (see section 4.4).

Tabulated list of adverse reactions
Undesirable effects observed in clinical studies with adrenal insufficiency patienst treated with hydrocortison (modified release or continuous subcutaneous hydrocortisone infusion) are displayed in the following table:

MedDRA system/organ class	**Undesirable effects**
Nervous system disorders	Vertigo, headache
Gastrointestinal disorders	Gastroenteritis, diarrhoea and nausea
Musculoskeletal and connective tissue disorders	Arthralgia
General disorders and administration issues	Fatigue
Cardiac disorders	Hypertrophic cardiomyopathy in prematurely born infants
Investigations	Weight increased

In addition the following adverse reactions have been reported for other hydrocortisone medicinal products given for indications other than adrenal insufficiency replacement therapy in higher doses (frequencies not known):

Immune system disorders
Activation of an infection (tuberculosis, fungal and viral infections including herpes)

Endocrine disorders
Induction of glucose intolerance or diabetes mellitus

Metabolism disorders
Salt and water retention leading to oedema, hypertension, hypokalaemia

Psychological disorders
Euphoria, psychosis, sleeplessness

Eye disorders
Increased intraocular pressure and cataracts

Intestinal disorders
Dyspepsia and worsening of a pre-existing ulcer

Skin disorders
Cushing-like symptoms, stretch marks, ecchymosis, acne and hirsutism, impaired wound healing

Musculoskeletal and connective tissue disorders
Osteoporosis with spontaneous fractures and muscle weakness

Immune system disorders
Hypersensitivity

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Acute overdose with hydrocortisone in patients with adrenal insufficiency has not been identified. No antidote is available. If adverse effects occur, symptomatic treatment should be initiated as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: glucocorticoid, ATC code: H02AB09

Hydrocortisone is a glucocorticoid and is the synthetic form of the hormone cortisol secreted by the adrenal cortex. Glucocorticoid binds to cytosolic glucocorticoid receptors leading to activation or suppression of protein synthesis, which among other things plays a role in the immune system. Glucocorticoids are necessary for the metabolism, the immune systems, the musculoskeletal system and homeostatic functions among other things. Hydrocortisone has salt retention properties and is used as a replacement therapy for adrenal insufficiency.

5.2 Pharmacokinetic properties

Absorption
Hydrocortisone is well absorbed from the gastrointestinal tract after oral administration and maximum plasma concentrations are reached approximately 1 hour after administration.

Distribution
In plasma, cortisol is bound to corticosteroid-binding globulin (CBG, also called transcortin) and albumin. The binding is approximately 90%. Hydrocortisone crosses the placenta and small amounts of the agent have been detected in breast milk.

Biotransformation
Hydrocortisone is metabolised in the liver and other tissues to hydrogenated and degraded products including dihydrocortisole and tetrahydrocortisole. Hydrocortisone is a substrate of CYP3A4 (see section 4.5).

Elimination
The metabolites are mainly excreted in the urine as glucuronides together with a very small amount of unchanged hydrocortisone. Hydrocortisone crosses the placenta and small amounts have been detected in breast milk. The elimination half-life is 1-2 hours.

Linearity/non-linearity
At a dose of 5 mg to 40 mg, the exposure to hydrocortisone is less than dose proportional. The most likely cause of this dose dependence is a higher first pass effect at higher doses. It is unclear whether exposure to hydrocortisone is time-dependent.

Pharmacokinetic/pharmacodynamic relationship(s)
Hydrocortisone is a supplement for the shortage of the body's own cortisol, therefore there is a direct pharmacokinetic/pharmacodynamic relationship.

Pharmacokinetics in liver and kidney patients
A delayed metabolism of hydrocortisone may occur in liver patients. This can lead to increased hydrocortisone concentrations. In renal patients delayed inactivation and elimination of hydrocortisone by the kidneys can lead to increased hydrocortisone concentrations. The clinical response to hydrocortisone should therefore be monitored closely in both liver and kidney patients.

5.3 Preclinical safety data

Reproduction toxicity studies on hydrocortisone in mice and rats have resulted in cleft palates and growth retardation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each <Acecort> film-coated tablet with the strength of 1 mg, 5 mg, and 10 mg contain:
Lactose monohydrate
Sodium starch glycolate
Magnesium stearate

In addition <Acecort> 1 mg contains:
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

In addition <Acecort> 5 mg contains:
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)
Sunset yellow FCF (E110)
Yellow iron oxide (E172)
Ponceau 4R (E124)

In addition <Acecort> 10 mg contains:
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)
Sunset yellow FCF (E110)
Allura red AC (E129)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

<Acecort> 1 mg film-coated tablets: 12 months
<Acecort> 5 mg, <Acecort> 10 mg and <Acecort> 10 and 5 mg film-coated tablets: 24 months

6.4 Special precautions for storage

Do not store above 25°C
Keep the PVC-PE-PVdC/Alu blisters in the outer carton in order to protect from light

6.5 Nature and contents of container

<Acecort> 5 mg, <Acecort> 10 mg and <Acecort> 1 mg film-coated tablets: 20, 30, 50 or 100 tablets per package.
One package of mutliple PVC-PE-PVdC/Alu blisters containing 10 film-coated tablets.

<Acecort> 10 and 5 mg film-coated tablets: 84 tablets per package
Combo-package: one foldable box containing 4 blister packs each containing 21 film coated tablets for one week. One blister contains 7 red 10 mg film-coated tablets (morning dose) and 14 orange 5 mg film-coated tablets (afternoon and evening dose).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ace Pharmaceuticals BV
Schepenveld 41
3891 ZK Zeewolde
The Netherlands
+31 36 547 40 93

8. MARKETING AUTHORISATION NUMBER(S)

To be found in SmPC per country

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

March 2023