



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Plenadren

International nonproprietary name: hydrocortisone

Procedure No. EMEA/H/C/2185

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.



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1 Background information on the procedure

1.1 Submission of the dossier

The applicant DuoCort Pharma AB submitted on 06 May 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Plenadren, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 October 2008.

The application concerns a hybrid medicinal product as defined in Article 10(3)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

Plenadren was designated as an orphan medicinal product EU/3/06/372 on 22 May 2006 in the following indication: treatment of adrenal insufficiency. The calculated prevalence of this condition was 4.5 per 10,000 EEA population.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Plenadren as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: [ema.europa.eu/Find Medicine/Human medicines/Rare disease designations](http://ema.europa.eu/Find_Medicine/Human_medicines/Rare_disease_designations).

The Applicant applied for the following indication: "Treatment of adrenal insufficiency in adults."

The legal basis for this application refers to Article 10(3) of Directive 2001/83/EC – hybrid application.

The application submitted is composed of administrative information, complete quality data, a clinical study comparing PK and safety with the reference medicinal product Hydrocortone and non-clinical and other clinical data based on the Applicant's own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Hydrocortone, 10mg, 20 mg, tablets
- Marketing authorisation holder: Merck Sharp & Dohme Ltd
- Date of authorisation: 23-02-1989
- Marketing authorisation granted by:
 - Member State (EEA) : UK
 - National procedure
 - Marketing authorisation number: PL 0025/5053, PL 0025/5054

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Hydrocortone, 10mg, 20 mg, tablets
- Marketing authorisation holder: Merck Sharp & Dohme Ltd
- Date of authorisation: 23-02-1989
- Marketing authorisation granted by: UK
 - National procedure
 - Marketing authorisation number: PL 0025/5053, PL 0025/5054

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Hydrocortone, 10mg, 20 mg, tablets
- Marketing authorisation holder: Merck Sharp & Dohme Ltd
- Date of authorisation: 23-02-1989

- Marketing authorisation granted by: UK
 - National procedure
 - Marketing authorisation number: PL 0025/5053, PL 0025/5054
- Bioavailability study number(s): 2006-0007084-89

Information on Paediatric requirements

Not applicable.

Information relating to Orphan Market Exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice

The Applicant received protocol assistance from the CHMP on 21 September 2006 and 22 March 2007. The Scientific Advice pertained to clinical aspects of the dossier. Furthermore, National scientific advice pertained to clinical aspects of the dossier was provided by Sweden on 30 May 2005.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Tomas Salmonson** Co-Rapporteur: **Robert James Hemmings**

- The application was received by the EMA on 06 May 2010.
- The procedure started on 23 June 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 September 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 September 2010.
- During the meeting on 21 October 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 October 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 February 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 March 2011.
- During the CHMP meeting on 14 April 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 07 June 2011.
- The SAG meeting of experts on 15 June 2011, convened to address questions raised by the CHMP.
- During the CHMP meeting on 21 June 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 08 July 2011.

- During the CHMP meeting on 19 July 2011, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20 July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Plenadren.

2 Scientific discussion

2.1 Introduction

Plenadren modified-release tablets contain the active pharmaceutical ingredient (API) hydrocortisone, the most commonly prescribed API in glucocorticoid replacement therapy. Endogenous glucocorticoids are produced in the cortex of the adrenal gland with the main glucocorticoid in man being cortisol. Patients with adrenal insufficiency (AI) therefore lack endogenously produced cortisol.

Adrenal insufficiency may be primary, as a result of a disease in the adrenal cortex, or secondary (central) due to an underlying hypothalamic-pituitary disorder. Primary AI is usually referred to as Addison's disease. The onset of AI may vary from insidious to an acute life-threatening situation with severe salt and water deficit, which leads to shock and death within hours if not treated adequately. Frequently reported symptoms associated with AI are asthenia, weakness, lethargy, easy fatigability, nervousness, irritability, apathy, dizziness, headache, myalgia, anorexia, weight loss, nausea, abdominal pain, vomiting and diarrhoea.

Replacement therapy with glucocorticoids is a life-long and life-saving treatment. However, there are studies indicating that current treatment may not be optimal. In population-based, retrospective, observational studies, the relative risk of death was more than 2-fold higher in patients with Addison's disease on currently available replacement therapy compared with the background population. Similar data have been reported in patients with hypopituitarism and secondary AI.

Patients with AI have also been found to have increased frequency of cardiovascular risk factors including abdominal obesity, hypertension, dyslipidaemia and reduced health-related quality of life and bone mineral density. A possible explanation is an inadequate glucocorticoid replacement therapy, e.g. an attenuated diurnal variation (increased evening and night time exposure) in the plasma cortisol profile which has been associated with abdominal obesity

The complex glucocorticoid system is hard to mimic during oral replacement therapy and the lack of a serum marker of the biological activity of cortisol makes the monitoring of replacement therapy difficult. The most commonly reported replacement regimen consists of 20-35 mg hydrocortisone administered in two or three divided doses per day. The multiple dosing may be associated with an increased risk of non-compliance.

The total daily maintenance dose of hydrocortisone in AI is insufficient during a stressful event. The current concept has been to instruct patients with AI to double their daily dose of hydrocortisone during a minor illness. During a major illness or when oral administration of hydrocortisone is less likely to be helpful such as during vomiting and/or diarrhoea, treatment in an emergency unit is advocated with administration of saline infusion and parenteral hydrocortisone.

Thus there is a need for alternative dosing regimens with the aim to more closely mimic the circadian profile of serum cortisol.

Plenadren is a modified-release tablet containing a larger amount of non-micronized hydrocortisone and an immediate release film-coating containing a smaller amount of micronized hydrocortisone.

The core tablet is a swelling/eroding matrix based on hypromellose as the polymer controlling the dissolution. Part of the hydrocortisone is included in the coating layer to attain a rapid absorption. The 5 mg tablet has a pink colour and the 20 mg tablet is white. Different colours are used in order to differentiate the strengths. The strengths contain the same excipients but there are differences regarding the amount and the proportions of hypromellose. The strengths are therefore not dose proportional.

The product is constructed to give a very rapid absorption from the immediate release part. The major part of the immediate release fraction should be released within 10 minutes. The target for the extended release fraction is a steady hourly release over the first 6-8 hours with the total dose to be released and absorbed within 16-18 hours after dose intake.

2.2 Quality aspects

2.2.1 Introduction

Plenadren is presented as modified-release tablets containing 5 mg and 20 mg of hydrocortisone as active substance. The other ingredients are hypromellose, cellulose microcrystalline, pregelatinised starch, silica colloidal and magnesium stearate. The other ingredients of the coating are macrogol, polyvinyl alcohol, titanium dioxide, iron oxide yellow, iron oxide red, iron oxide black and talc. The medicinal product is packaged in HDPE bottles with polypropylene screw cap and packed in cartons.

2.2.2 Active Substance

The chemical name of hydrocortisone is $11\beta,17\alpha,21$ -trihydroxypregn-4-ene-3,20-dione corresponding to the molecular formula $C_{21}H_{30}O_5$ and relative molecular mass 362.5. The structure of this active substance is described in figure 1. It appears as white to almost white, crystalline and not hygroscopic. It is practically insoluble in water, sparingly soluble in acetone and in alcohol and slightly soluble in methylene chloride. Only one polymorphic form is consistently formed during the active substance production and used in the manufacture of the finished product. This active substance is described in the Ph.Eur.

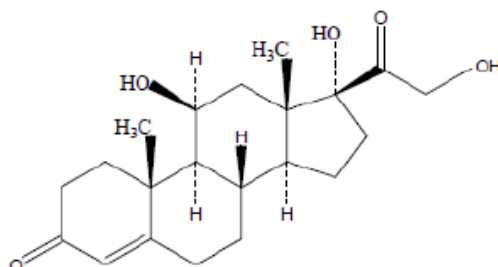


Figure 1: Hydrocortisone

The chemistry, manufacturing and control information on hydrocortisone has been evaluated by the EDQM and a European Certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP) has been issued. It was noticed that two additional supplementary tests (Other impurities, particle size and residual solvents) were included in the CEP.

Specification

Hydrocortisone is described in the European Pharmacopoeia. The Ph.Eur. specifications have been implemented by both active substance and finished product manufacturers, where applicable, to control the quality of the active substance. Additional specifications (other impurities, particle size and residual solvents), which were mentioned in the CEP were considered. The specification also complies

with ICH Q3A and includes tests for appearance (visual), identification (HPLC, IR), optical rotation (Ph.Eur.), loss on drying (Ph.Eur.), residual solvents (GC), particle size, impurities (HPLC), chromium and crystal form. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines. In general analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been provided and show consistent compliance with the predefined active substance specification.

Stability

The stability results from long-term (25°C/60%RH), accelerated (40°C/75%RH) and stress studies were completed according to ICH guidelines and demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: hydrocortisone dried basis (Ph.Eur.), loss on drying (Ph.Eur.), appearance (visual) and impurities (HPLC). It was noticed that the test methods applied are those used for release of the active substance. It can be concluded that the proposed re-test is justified based on the stability results when the active substance is stored in the original packing material.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

All information regarding the choice of the active substance and the excipients are sufficiently justified. The main aim of the pharmaceutical development was to formulate modified-release tablets. The composition of the modified-release tablets have not changed during the development and clinical trials, except for a small reduction in the amount of colourants. This minor change in the composition does not have any impact in the safety and efficacy of the finished product. It is important to emphasise that both tablet strengths contain the same components but differ regarding amount and proportions of the two viscosity grades. The immediate release coating consists of a part of the active substance, which is included in the coating layer to attain a rapid absorption of hydrocortisone. It was noted that the excipients selected for this formulation are commonly used in pharmaceutical formulations. The direct compression was selected for manufacturing the core tablets. During the pharmaceutical development critical formulation and manufacturing parameters were identified and adjusted. The dissolution method developed is able to identify differences in the amount of drug release from the core tablets, coated tablets and placebo core tablets.

Manufacture of the product

The proposed commercial manufacturing process for the modified-release tablets involves standard technology and it is divided into the following phases:

- The manufacturing of the core tablets, which consists of two steps: mixing and compression.
- The film-coating process, which consist of the following steps: mixing and film coating.

The manufacturing process has been adequately described and some steps have been identified and control. Four critical parameters were identified and optimised during the drug development (spray rate, amount of the sub coat, percentage of the active substance in the coating suspension and compression). It was noticed that the manufacturing process has been adequately validated for three production scale batches of each strength. Furthermore, the validation protocol proposed for the full

scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing.

Product Specification

The product specification is standard for as modified-release tablets and contains tests with suitable limits for appearance, identification of hydrocortisone (HPLC, FTIR), assay (HPLC), impurities (HPLC), uniformity of dosage units (Ph.Eur), dissolution and microbiological purity (Ph.Eur). Impurities and degradation products identified are those described in the European Pharmacopoeia and in the CEP. No new degradation products are formed during the manufacturing or storage of the finished product. All analytical procedures that were used for testing the finished product were properly described and satisfactorily validated in accordance with the relevant ICH guidelines. The batch analysis data for 4 production scale batches of each strength confirm that the finished product can be manufactured reproducibly according to the agreed finished product specifications.

Stability of the product

Stability studies under ICH long-term, intermediate and accelerated conditions (i.e. 25°C/60% RH, 30°C/65% RH and 40°C/75% RH) have been carried out on four batches of 5 mg modified-release tablet and three batches of 20 mg modified-release tablet. The following parameters were monitored during the stability studies: appearance, assay, related substances, dissolution of hydrocortisone and microbiological quality. The analytical methods used for the stability studies are identical with the methods proposed for routine testing of the finished product. During the stability studies the product did not show any significant change in its quality. All the results remained well within the specification limits during all the stability studies. Results for bulk stability studies of all strengths were also acceptable.

A Photostability testing programme was conducted on one batch of each dosage strength in accordance with the recommendations of ICH guideline Q1B. The results were found to meet the specifications and the finished product does not require any special light protection.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4 Discussion on chemical, and pharmaceutical aspects

Hydrocortisone is described in the European Pharmacopoeia. Where applicable, specifications applied by both the active substance and the finished product manufacturers are in-line with the monograph. Additional specifications (other impurities, particle size and residual solvents), which were mentioned in the CEP were considered. The pharmaceutical development of the formulation, the manufacturing process, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated for three production scale batches of each dosage strength at the proposed manufacturing site. Furthermore, the validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing. The routine specifications and tests methods proposed for the finished product will adequately control the quality of the finished product. Analytical methods were well described and validated in agreement with relevant guidelines.

Batch analyses were presented and the results showed that the finished product meets the specifications proposed.

The container-closure systems for both pharmaceutical forms were found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for finished were adequately established.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished products have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the medicinal product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, all quality issues have been resolved.

2.3 Non-Clinical aspects

2.3.1 Introduction

Hydrocortisone (Plenadren) modified-release tablet contains a synthetic glucocorticoid which is the pharmaceutical form of the endogenous glucocorticoid, cortisol. It has, like other corticosteroids anti-inflammatory, antipruritic and vasoconstrictive properties and important metabolic actions of which the best known is on carbohydrate metabolism. Hydrocortisone has been marketed in Europe, Canada and US for several decades mainly as replacement therapy in adrenal insufficiency and for the topical treatment of dermatoses, such as eczematous dermatitis.

Hydrocortisone (Plenadren) modified-release tablet is indicated for replacement treatment of adrenal insufficiency, including both primary adrenal insufficiency (usually referred to as Addison's disease), and secondary adrenal insufficiency (usually part of a more general pituitary dysfunction or hypopituitarism). The proposed indication is treatment of adrenal insufficiency in adults. The recommended doses are 15-40 mg depending on bodyweight. However, the dose is individualised according to the clinical response to the lowest possible maintenance dose, the most commonly used dose being between 20-30 mg per day.

The modified-release tablet is composed of an extended-release (ER) core (gellifying matrix type) coated by an immediate-release (IR) layer; two tablet strengths are available 5 and 20 mg allowing flexibility in dosing e.g. in patients with higher dosing.

The modified-release tablet is designed for once daily administration and is stated to give a better concentration-time profile similar to that of the physiological cortisol profile, and without the peaks and troughs seen with the twice or thrice daily dosing of the conventional hydrocortisone tablets.

The pharmaceutical excipients (see below) are well known and commonly used in the pharmaceutical industry and fulfil the requirements of Ph.Eur. List of excipients:

Hypromellose

Cellulose, microcrystalline

Pregelatinised starch

Silica, colloidal, anhydrous

Magnesium stearate

Macrogol

Polyvinyl alcohol

Talc

Titanium dioxide (E171)

Hydrocortisone is a substance with long experience of use in man. For such compounds the overall supportive information is usually based on a combination of pharmaco-toxicological data from literature, scientifically accepted monographs and data from clinical trials, as well as results of post-marketing experiences in man. The non-clinical part of this application is therefore based on data from the published literature, which is acceptable. The Applicant has also reviewed the information available on the assessment of the maximum residue levels (MRL) of hydrocortisone in food producing animals (the Summary report of hydrocortisone (*EMEA/MRL/377/98-Final*)) performed by the Committee of Veterinary Medicinal Products (CVMP), the European Assessment Report (EPAR) for Easotic and the Summary of Product Characteristics of Hydrocortone.

GLP aspects

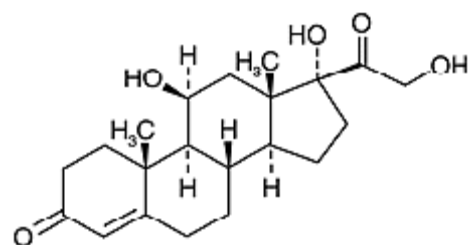
The non-clinical dossier comprises published literature, much of which predates the establishment of Good Laboratory Practice (GLP). There is little or no information about GLP compliance of the toxicity studies underlying the referred publications, which is accepted considering the well known toxicological properties of hydrocortisone.

2.3.2 Pharmacology

Primary pharmacodynamic studies

No non-clinical pharmacology studies have been performed with Hydrocortisone (Plenadren) modified-release tablets, which is acceptable. Hydrocortisone is a synthetic glucocorticoid and the pharmaceutical form of the major endogenous glucocorticoid in man, cortisol. Thus, the pharmacological effects of hydrocortisone in man are identical to cortisol e.g. metabolic actions on carbohydrates, proteins and fat as well as anti-inflammatory and immunosuppressive actions and effects on brain function.

Structure of the active substance



11β,17α,21-Trihydroxypregn-4-ene-3,20-dione

The molecular weight is 362.47 g/mol. The aqueous solubility - at three different pH 6.5, 3.5 and 1.2 - is respectively 0.35, 0.38 and 0.37 mg/ml and the solubility in ethanol at 5 and 25 C is 13.39 and 15.40 mg/ml, respectively.

In contrast to man, the major glucocorticoid in rats and mice is corticosterone, which is secreted almost exclusively. In dogs cortisol and corticosterone are secreted in approximately equal amounts.

Cortisol is predominantly produced in the adrenal cortex (*Oelkers 1996; Arlt et al 2003*). The production and secretion of cortisol are governed by a complex and highly efficient system that includes the hypothalamus, pituitary and the adrenal glands, i.e., the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol is secreted in a circadian release rhythm regulated by the suprachiasmatic nucleus of the hypothalamus. Several physical and psychological stressors also activate the HPA axis through enhanced activity of the hypothalamus thus increasing serum cortisol concentration. The hypothalamus produces corticotropin-releasing hormone (CRH), which in turn acts on the pituitary, to produce adrenocorticotropic hormone (ACTH). ACTH affects the adrenal cortex, which responds with increased production and secretion of cortisol. The estimated number of secretory bursts of ACTH is 40 per 24 hours (*Veldhuis et al 1990*) and it is the amplitude of each burst that gives rise to the 24-hour rhythm in circulating cortisol. Approximately 15 minutes after each burst of ACTH there is a surge of cortisol (*Horrocks et al 1990*) released into the circulation. This pulsatility secretion pattern has been reported in all species studied including rat, rhesus monkey, Syrian hamster, horse, sheep and goat (*Lightman et al 2008*). This pulsatility pattern is physiologically very important, for example does flattened diurnal rhythm attenuate the 5-HT_{1a} function and reduce the effectiveness of selective serotonin reuptake inhibitor (SSRI) treatment in rodents and there is an attenuation of the diurnal variation of serum cortisol levels in patients with depression (*Lightman et al 2008*).

All tissues contain and express the glucocorticoid receptor (Type I). Cortisol has similar affinity to the mineralocorticoid (Type II) receptor, which in turn is defended by 11 β hydroxysteroid dehydrogenase (HSD) type 2 that converts active cortisol to inactive cortisone. The enzyme 11 β HSD has two isoforms, one (type 2) in the kidney, salivary gland and placenta that converts cortisol to cortisone and a second isoform (type 1) mainly located in adipose tissue, skeletal muscle and liver that converts cortisone to cortisol. In rats, it has also been demonstrated that at the peak of each corticosterone pulse the activated glucocorticoid receptor is translocated into the nucleus to exert its effects. At the trough of each pulse the glucocorticoid receptor is cleared from the nucleus by a proteasome mediated mechanism (*Conway-Campbell et al 2007*), while the mineralocorticoid receptors are retained in the nucleus. Thus, the glucocorticoid action is governed by the HPA axis, the glucocorticoid receptor, nuclear clearance and the activity of 11 β HSD at the tissue level.

The main metabolic effects of cortisol are on carbohydrate and protein metabolism. The metabolic effects are essentially anabolic in the liver and catabolic in muscle and fat. Cortisol also has mild lipolytic effects. The overall metabolic effect of cortisol is to increase blood glucose concentrations by increased gluconeogenesis, promote lipolysis and increase catabolism of proteins from muscle. (*Nussey et al 2001*).

Cortisol, like other glucocorticoids (GC's), exerts its anti-inflammatory activity by binding and activating the cytosolic glucocorticoid receptor. The receptor-ligand complex may translocate itself into the nucleus of the cell, where it binds to glucocorticoid response elements (GRE) in the promoter region of the target genes resulting in the regulation of gene expression and gene suppression. This transactivation leads to an upregulation of the anti-inflammatory lipocortin 1 and p11/calpactin binding protein (*Newton 2000*). The opposite effect, transrepression, also occurs and here the activated ligand-receptor complex interacts with transcription factors such as AP-1 and NF- κ B, which act on non GRE-containing promoters and prevent the transcription of pro-inflammatory genes such as IL-1, IL-4, IL-5, IL-8, chemokines, cytokines, GM-CSF and TNF-alpha (*Newton 2000*). In addition to these two mechanisms, the glucocorticoids have been shown to have a number of activities that are independent of regulation of gene transcription (*Croxtall et al 2002*).

Physiologic levels of glucocorticoids (GCs) are essential for efficient brain functions for neuronal growth, differentiation, survival and they positively modulate synaptic plasticity (*Fietta et al 2009*). GCs control appetite, food-seeking and feeding behaviour as well as influences chronobiologic awakening/sleeping rhythm. Increases in GCs stimulate feeding and may induce arousal and insomnia. Physiologic levels of GCs play an essential role in cognitive functions and acute increases in cortisol levels can reversibly impair long-term memory functions, and inhibit traumatic memory retrieval. Hypercortisolemia (Cushing's disease) or excessive doses of synthetic corticosteroids can cause psychiatric disturbances. The psychic effects have been found to range from an initial slight increase in the overall sense of well-being or low-grade mood changes up to severe psychiatric disorders and suicidality.

Also, >90% of circulating cortisol is bound to plasma proteins mainly corticosteroid-binding globulin (CBG) affecting the availability of the steroid. The hepatic CBG synthesis is influenced by oestrogen and is therefore increased during pregnancy when there are markedly elevated serum levels of oestrogen (*Sandberg et al 1959, Sandberg et al 1960*) and also during oral oestrogen treatment due to the first pass metabolism in the liver (*Qureshi et al 2007*).

In accordance with these mechanisms, hydrocortisone has metabolic actions on carbohydrates, proteins and fat as well as anti-inflammatory, immunosuppressive and vasoconstrictive properties and effects on brain function.

Secondary pharmacodynamic studies

Chronic exposure to excessive concentrations of endogenous cortisol or to pharmacological doses of glucocorticoid (GC) (*Manelli et al 2000*) causes osteopenia, osteoporosis and bone fracture. The mechanism of the reduction in bone formation is complex and includes both direct and indirect effects. There is a direct inhibitory effect on osteoblasts, depleting the cell population capable of forming new bone, and a decrease of type 1 collagen synthesis and modulation of the expression of mRNA encoding osteopontin, fibronectin, b-integrin and bone sialoprotein thereby inhibiting bone matrix synthesis. The mechanism also involves an indirect effect mediated by a number of local growth factors. The effects of GCs on bone resorption are still not clearly understood, but histomorphometric studies have suggested an increase in bone resorption. It has been hypothesised that GC decrease bone resorption via an increase in the rate of receptor-mediated apoptosis of or inhibitory action on osteoclasts. An indirect action is that GC's decrease net intestinal Ca^{2+} absorption and increases renal excretion of Ca^{2+} in both humans and animals, but the mechanism is not known although an inhibitory action on the vitamin D action has been suggested. Other effects that might influence in the pathogenesis of GC-induced osteoporosis are the inhibitory effects of GCs on growth hormone (GH) secretion, inhibition of the hypothalamic-pituitary-gonadal axis, effects on PTH secretion and contribution to alterations in vitamin D metabolism.

Other effects of hydrocortisone are inhibition of corticotropin-releasing hormone resulting in inhibition of ACTH via feed-back mechanism. GC:s also increase blood pressure by increasing the sensitivity of the vasculature to epinehrine and norepinehrine, and reducing the histamin secretion. In dogs, kidney diuresis is controlled by cortisol (*Boykin et al 1978*) and humans have a similar mechanism (*Dingman et al 1965*).

Safety pharmacology programme

No non-clinical safety pharmacology studies have been performed with Hydrocortisone (Plenadren) modified-release tablets, which is acceptable.

The effects of hydrocortisone on systemic arterial blood pressure and urinary protein excretion were investigated in dogs (*Schellenberg et al 2008*). Six dogs were given 8 mg/kg hydrocortisone orally twice daily (q 12) for 12 weeks and six dogs served as control dogs and were given placebo. Before, during and after dosing blood pressure (BP), urine protein: creatinine ratio (UPC), microalbuminuria (MALB), urine albumin : creatinine ratio (UAC), and urine gel electrophoresis were evaluated. During hydrocortisone administration BP and UPC increased substantially, from 123 mmHg (range 114–136 mmHg) and 0.17 (0.15–0.28) to a maximum of 143 mmHg (128–148 mmHg) and 0.38 (0.18–1.78), respectively, on day 28. MALB developed in four dogs and UAC increased significantly in all dogs during hydrocortisone administration with the maximum on day 84. Both increases in BP and proteinuria were reversible and completely resolved within one month after the end of dosing. SDS-PAGE revealed the proteinuria to be primarily albuminuria with a pronounced increase during hydrocortisone treatment. Furthermore, a protein of 25–30 kDa was found in male dogs, identified by mass spectrometry to be arginine esterase, the major secretory prostatic protein. In conclusion, long-term hydrocortisone treatment with excessive doses resulted in significant but mild increases in systemic BP and urinary protein excretion in dogs after oral treatment. The effects were reversible within one month after discontinuation of hydrocortisone.

There is limited information in the literature on the effects of hydrocortisone on vital organ systems of animals such as the central nervous, cardiovascular and respiratory system. However, the clinical experience from hydrocortisone is extensive and the pharmacological effects on the vital organs are well known. The risks associated with hydrocortisone treatment are appropriately addressed in the Plenadren SmPC.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed with Hydrocortisone (Plenadren) modified-release tablets, which is acceptable. Possible interactions with other drugs are mainly related to the metabolism and excretion of hydrocortisone (see also Pharmacokinetic drug interactions below).

2.3.3 Pharmacokinetics

Pharmacokinetic studies

No non-clinical pharmacokinetic studies were performed using Hydrocortisone (Plenadren) modified-release tablets and there is only limited information available on the absorption, distribution, metabolism and excretion (ADME) of hydrocortisone in animals in the published literature.

Methods of analysis

The analytical methods for hydrocortisone in biological fluids are considered well established.

Absorption

Hydrocortisone is classified as a class II drug (high permeability and low solubility) according to the biopharmaceutical classification system (BCS) (*Nayler et al 1993, Pedersen 2000, Amidon 1995*). In rats it has been reported that the fraction of the dose absorbed from the intestine is 93% and the intestinal permeability was high (*Dowty et al 1997, Heimbach et al 2003*). There is a high correlation between human and rats regarding intestinal permeability (*Fagerholm et al 1996*).

In male rats of the Sprague-Dawley strain the absorption of ¹⁴C-hydrocortisone was investigated after intravenous, intramuscularly, sublingual and gastric administration. It was concluded that the varying

route of administrations of ^{14}C -hydrocortisone to rats caused different excretion rates of the radiolabelled metabolites, but the amounts excreted were independent of the route of administration (Hyde *et al* 1957). This indicates that the absorption is complete from all administrations sites.

The transdermal penetration and skin retention of hydrocortisone was investigated on canine skin samples (Mills *et al* 2005). The skin samples were obtained from the thorax, neck and groin regions. The vehicles used were PBS solution (PBSS) alone, 50% ethanol (EtOH) in PBSS (wt/wt), and 50% propylene glycol in PBSS [wt/wt]. Saturated solutions of hydrocortisone that contained trace amounts of radiolabelled ^{14}C -hydrocortisone in each vehicle were applied to the stratum corneum of each skin sample, and aliquots of receptor fluid were collected for 24 hours and analysed for hydrocortisone. Penetration of topically applied hydrocortisone was enhanced when EtOH was used in vehicle formulation. Significant regional differences were also found.

In the skin from horses (Mills *et al* 2006) taken from the thorax, groin and leg (dorsal metacarpal) regions, the penetration of radiolabelled ^3H -hydrocortisone, in a saturated solution of unlabelled hydrocortisone in 50% ethanol (w/w) which penetrated through and remained within skin samples was measured over 24 hr. Significantly higher ($P < 0.001$) maximum flux was measured when hydrocortisone was applied to skin from the leg, compared to thorax and groin, although significantly less hydrocortisone ($P < 0.001$) was retained within skin from the leg at 24 hr.

Distribution

The plasma concentration-time profile followed a typical two compartment model after an intravenous bolus injection of 50 mg/kg hydrocortisone to rats (Mager *et al* 2003). The distribution phase was very rapid with a distribution half-life of about 8 minutes. The volume of distribution at steady-state (V_{ss}) was 1.24 ± 1.1 l/kg (Mager *et al* 2003) and the central volume of distribution was 0.57 ± 12 l/kg.

In pregnant mice, the distributions of the glucocorticoid ^{14}C -hydrocortisone and the mineralocorticoid ^{14}C -deoxycorticosterone were compared with that of the natural murine hormone ^{14}C -corticosterone by whole-body autoradiography at 12.5 days of gestation (Waddell *et al* 2005). The patterns of distribution were similar for the three compounds. At 3 h after injection the highest concentrations of radioactivity were in maternal liver, bile, intestinal contents, kidney and urine and uterine luminal fluid. Radioactivity in embryos was less than that in most maternal tissues. Embryonic brain had a slightly higher content. The embryonic palatal buds had not higher amount of radioactivity than other embryonic tissues. The author concludes, that the intense accumulation in the uterine lumen of all of the compounds suggests a secretory mechanism by the yolk sac that is not specific for a particular steroid.

Metabolism

In rats, following intravenous bolus injection of 50 mg/kg hydrocortisone, the plasma concentration-time profile followed a typical two compartment model (Mager *et al* 2003). The total clearance (based on plasma concentrations) was about 40 ml/min/kg and the terminal half-life was 1.28 ± 1.6 hr.

The subcellular distribution of ^3H -hydrocortisone and its metabolites in the liver and kidney was investigated in normal and diabetic rats (Minchenko *et al* 1988). Ten minutes after administration several metabolites (mostly tetrahydrocortisol) and the native hormone were found in liver cytosol, microsomes, mitochondria and nuclei, the relative content of individual compounds in various subcellular fractions being different. Ten minutes after administration several metabolites (mostly tetrahydrocortisol) and the native hormone were found in liver cytosol, microsomes, mitochondria and nuclei, the relative content of individual compounds in various subcellular fractions being different. In liver mitochondria, microsomes and nuclei of alloxan diabetic rats, the concentration of

tetrahydrocortisol was decreased, while that of native hormone was increased as compared to normal animals. In kidney cytosol and microsomes of intact rats, cortisone and tetrahydrocortisol were found. In diabetic animals, however, the concentration of tetrahydrocortisol increased, while that of cortisone was undetectable.

In adrenalectomised dogs, hydrocortisone was infused intravenously during steady state conditions at rates selected to cause increasing levels of systemic hydrocortisone concentration. Blood samples were obtained for measurement of hydrocortisone clearance and for measurement of the metabolic clearance rate (*McCormick et al 1974*). A hydrocortisone disappearance curve was obtained after cessation of the infusion and the half-time and fractional disappearance rate calculated from the curve. All quantitatively significant hydrocortisone metabolisms occurred in the kidney (18%), liver (46%) and gastrointestinal tract (36%). The calculated metabolic clearance rate was 521 ml/min, or 18 ml/min/kg. The clearance of hydrocortisone by individual organ systems and the total metabolic clearance of hydrocortisone by the animal were linear processes. The hydrocortisone disappearance curve itself was nonlinear on semi logarithmic coordinates and consisted of at least two components.

Excretion

After administration of ¹⁴C-hydrocortisone, intramuscularly, sublingually and intragastrically to male rats more than half of the total radioactivity given was recovered in the faeces and the remainder in the urine (*Hyde 1957*). The rate of excretion was greatest after intravenous administration and decreased in order with sublingual, intramuscular and intragastric routes of administration. However, the amounts eliminated via the bile, urine and faeces were independent of the route of administration.

Results from the summary report (*EMEA/MRL/377/98-Final*) indicate that in rats, following subcutaneous administration of 0.5mg/kg bw ¹⁴C-hydrocortisone, 74-89% of the administered dose was recovered in the faeces within 24 hours. In guinea pigs, a rapid excretion was observed mainly in the urine.

No reports describing the excretion of hydrocortisone into human milk have been located. However, endogenous cortisol is excreted in the breast milk, which makes it reasonable to assume that this is relevant also for hydrocortisone (*Rosner et al 1976, Kulski et al 1981*).

Pharmacokinetic drug interactions

No non-clinical pharmacokinetic drug interaction studies have been performed using Hydrocortisone (Plenadren) modified-release tablets.

Other drugs may affect cortisol clearance by inducing or inhibiting the various enzymes involved in the metabolism of cortisol, such as CYP 3A4 and other specific steroid enzymes. The possible interactions resulting from co-administration of such drugs are covered in the proposed Plenadren SmPC.

Other pharmacokinetic studies

No other non-clinical pharmacokinetic studies have been performed using Hydrocortisone (Plenadren) modified-release tablets, which is acceptable.

2.3.4 Toxicology

Single dose toxicity

According to the summary report (*EMEA/MRL/377/98-Final*) single dose toxicity studies were carried out in rats and mice. However, only figures for the rat studies are presented. Rats were dosed either subcutaneously or intraperitoneally with hydrocortisone. Many rats died during the second week of recovery due to infections, which might be related to the immunosuppressive effects of hydrocortisone. In both rats and mice the pathological effects observed were reduced adrenal weights, liver damage, lung consolidation and gastrointestinal effects.

Repeat dose toxicity

No standard repeat-dose toxicity studies were presented in the summary report (*EMEA/MRL/377/98-Final*). An eight days repeat-dose toxicity study in rabbits to investigate the possible hepatotoxicity was described. Animals were given 10 or 15 mg/kg/animal of hydrocortisone or 25 mg/animal of hydrocortisone acetate intramuscularly per day for eight consecutive days. In all treated groups hepatotoxicity was observed with increased liver weights, focal hepatic necrosis and increased glycogen deposition. After a recovery period of 20 days the liver weights were comparable to control animals.

No information regarding toxicokinetics or interspecies comparisons have been provided, which is considered acceptable.

Genotoxicity

In the summary report (*EMEA/MRL/377/98-Final*) it is concluded that hydrocortisone was not mutagenic in an *in vitro* assay in *Salmonella typhimurium* TA97a, TA98, TA100 or TA1535 in the presence or absence of metabolic activation. Positive results were obtained in an *in vitro* chromosomal aberration test, but without dose response in the tested range (1 – 50 µg/ml). A dose related increase in micronuclei was found in mice given 1, 10 and 100 mg/kg bw of hydrocortisone and positive results were also found in an *in vivo* sister chromatid exchange analysis in the bone marrow of mice given single intraperitoneal injections of hydrocortisone 0.1, 1 and 10 mg/kg bw. CVMP points out that all of the positive results were reported in a single published report and no information of the purity of the compound tested was provided. No reference is provided, however, the tests and results are identical with a report published in 1990 (*Bali et al 1990*). CVMP also points out that the results from this study conflict with the negative results from mutagenicity studies carried out with the synthetic corticoid steroids dexametasone, prednisolone and methylprednisolone. Furthermore, these results also conflict with the results for hydrocortisone acepoate (HCA). A complete set of *in vitro* and *in vivo* genotoxicity tests was carried out (genetic mutation, chromosomal aberration and micronucleus test) for this compound. All the studies were conducted according to GLP requirements and were in line with the appropriate guidelines. No evidence of mutagenicity was seen. These studies were provided in the dossier for the veterinary pharmaceutical Easotic and were evaluated by CVMP (*EPAR Easotic*).

The positive findings in the old genotoxicity studies in mice, which indicate a clastogenic potential of hydrocortisone are considered questionable. Later studies and the extensive clinical use do not indicate a clastogenic potential of hydrocortisone.

Carcinogenicity

No carcinogenicity studies have been identified in the literature, however an abstract of a life span study in rats (*Schmähl et al 1976*) has been located. The study included life-long treatment in the rat and included several compounds of which one was hydrocortisone. No evidence of a carcinogenic potential was found for hydrocortisone. No details of the study were available.

Reproduction Toxicity

The effects of hydrocortisone during the prenatal period on the fertility and sexual behaviour in male rats were investigated (*Pereira et al 2003*). Pregnant rats were treated subcutaneously with hydrocortisone acetate, at 1.5 mg/day on day 17-19 of gestation. In the male offsprings a decreased body weight was observed, but no alteration in anogenital distance. As adults, reductions of body weight, plasma testosterone levels, and seminal vesicle wet weight without secretion were observed. No alterations in the wet weights of the testes, epididymis, and seminal vesicle with secretion were seen. The males were able to mate with normal females, which became pregnant, however an increased number of post-implantation losses were seen. After castration and pre-treatment with exogenous oestrogens decreased male sexual behaviour and the appearance of female sexual behaviour were seen.

In another study (*Piffer et al 2004*), pregnant rats were treated subcutaneously with hydrocortisone acetate, at 1.5 mg/day on day 17-19 of pregnancy. Immediately after delivery, in both the treated mothers and in respective pups at birth, reduced adrenal wet mass and plasma corticosterone levels were found, which may indicate impairment of the hypothalamus-pituitary-adrenal (HPA) axis. In puberty, the oestrous cycle and fertility was affected in the offspring.

A number of studies have described the effects of hydrocortisone on the pregnancy outcomes in laboratory animals.

Pregnant mice from a genetically susceptible strain were treated with 2.5 mg/day hydrocortisone intramuscularly for 4 days starting on the 10th or 11th gestational day (*Shepard 2004*). Hydrocortisone was shown to produce cleft palate in the offspring at an incidence similar to that of cortisone (95%) in pregnant mice. No other gross external malformations were observed in the offspring.

In pregnant mice, the potential to produce cleft palate was studied following therapeutically equivalent intramuscular doses of hydrocortisone (4 mg), prednisolone (1 mg), or dexamethasone (0.15 mg) administered on gestational days 9-14 (*Pinsky et al 1965*). The frequency of cleft palate with the three corticoids was 18%, 77%, and 100%, respectively. The differences in the potential to induce cleft palates in the foetuses can be explained by differences in the metabolism of the compounds in the placenta. Hydrocortisone is metabolised to inactive cortisone by 11 β -hydroxysteroid dehydrogenase (HSD) type 2, which is present in the placenta. 11 β HSD type 2 does not metabolise dexametasone and to a lesser degree does prednisolone.

In another study, three levels of hydrocortisone sodium succinate, 0,3,15, and 30x, (300, 1500 and 3000 mcg/animal/day, respectively) were ophthalmically applied to pregnant CD-1 mice on days 10-13 of gestation and at Day eighteen the foetuses were removed by caesarean section and examined for malformations. The incidence of cleft palate was significantly higher ($p < 0.05$) in the medium- and high-dose treatment groups than in either the low-dose treatment group or saline-treated controls (52.8 and 73.2 % vs 9.2 and 0 %, respectively). There was no significant difference in the incidence of foetal deaths and resorptions between drug-treated and control foetuses (*Ballard et al, 1975*). The

author also refers to other studies in mice performed with hydrocortisone by the systemic route, which produced teratogenic effects such as cleft palates, cataracts, and foetal resorptions.

In rabbits, it was demonstrated that a subcutaneous dose of 250 mg/kg of hydrocortisone on gestational days 11 through 17 could induce polycystic kidney disease in the foetuses (*Crocker et al 1991*).

In rabbit foetuses, given a 2mg intramuscular injection of hydrocortisone on gestational day 24, reduced lung and body weights were observed (*Kotas et al 1974*). Treated foetuses also had fewer lung cells as indicated by decreased DNA per lung. A full recovery was seen within 30 days of birth.

The summary report of hydrocortisone (*EMEA/MRL/377/98-Final*) describes a number of studies performed to investigate the induction of clefts palates in the foetuses of hydrocortisone treated dams. In pregnant hamsters, intramuscular doses of 15-50 mg/kg of hydrocortisone induced cleft palates. In rabbits, ocular administration of 1.2 or 1.8 mg/animal of hydrocortisone were teratogenic. In mice, ocular administration caused dose related incidence of cleft palates in the foetuses with a NOEL of 0.18 mg/animal. The EPAR for Easotic (one of the active ingredients is hydrocortisone aceponate (HCA) describes briefly a series of four older studies performed with HCA- all by the subcutaneous route – examining the organogenesis in pregnant rat and rabbit and the peri- and post-natal development in rat. In the study in rabbits, the hydrocortisone base was also used and induced similar embryotoxicity in the offspring at 0.48 mg/kg *per* ocular route as a subcutaneous dose of HCA at 0.33 mg/kg.

In summary, the available reproductive toxicity data demonstrate, although the data are old and not performed according to current guidelines, the well-known fact that hydrocortisone in high doses, like other corticosteroids, has a teratogenic and embryotoxic potential in laboratory animals.

Local Tolerance

Not applicable since oral administration applies for Plenadren.

Other toxicity studies

No further studies to investigate antigenicity, immunotoxicity, dependence, metabolites and impurities have been reported, which is acceptable.

Hydrocortisone (DuoCort) contains two qualities of hydrocortisone; micronized and non-micronized. The impurities potentially present in lots of hydrocortisone are listed below. All of these impurities are potential process impurities. The specifications of the impurities comply with the specifications in Ph.Eur. for hydrocortisone with the additional specifications listed in the Certificate of Suitability, R0-CEP 2002-220-Rev 03, regarding impurity G, unsymmetrical dimer, 9(11) epoxide and methanol. Hydrocortisone micronized and non-micronized are manufactured/synthesized under the same process and include the same impurities. The only difference is that the micronized material undergoes an additional micronizing step.

The specifications of these impurities are shown below:

Impurities Total	≤2.0%
Imp A (Prednisolone)	≤0.2%
Imp B (Cortisone)	≤0.2%
Imp C (Hydrocortisone Acetate)	≤0.5%
Imp D	≤0.5%

Imp E	≤0.5%
Imp F	≤0.3%
Imp G (21- Aldehyde)	≤0.4%
Imp H	≤0.15%
Imp I	≤0.5%
Imp N (Symmetrical Dimer)	≤0.15%
9(11)-epoxide	≤0.3%
Unsymmetrical Dimer	≤0.3%
Unspecified	≤0.20%

The specifications of the impurities for the modified-release tablets, 5 and 20 mg, are the same as for the Active Pharmaceutical Ingredient at release and for shelf-life with the exception of Impurity G. The specification of Impurity G is ≤ 0.4 % at release and ≤ 0.5 % at the end of shelf-life. With regards to residual solvents, hydrocortisone complies with the ICH Q3C guidelines.

2.3.5 Ecotoxicity/environmental risk assessment

An environmental risk assessment for hydrocortisone has been conducted by the Applicant.

The $PEC_{\text{surfacewater}}$ has been calculated to be 0.00662 µg/L using a $DOSE_{ai}$ of 40 mg.inh⁻¹.d⁻¹ and default values for $WASTE_{inhab}$ and $DILUTION$ and this is below the EMEA action limit of 0.01µg/l.

The F_{pen} value has been refined based on the following assumptions: The incidence of the disease i.e. the maximum number of patients that can be treated by Plenadren are 33.1 in a population of 100,000 inhabitants. Thus, out of a population of 500,000,000 in Europe (EU27) a maximum number of 165,500 can be treated with Plenadren per year. The maximum daily dose is 40 mg/day over 365 days. Therefore the total amount of Plenadren used over a year in the EU is 2416.6 kg. Using the calculation in the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00) an F_{pen} value of 0.00031 % is calculated. Therefore, a Phase II assessment is not considered necessary. The $\log K_{ow}$ of hydrocortisone is below the threshold of 4.5 and consequently further investigation of the potential for persistence and bioaccumulation are not necessary. No other environmental concerns are apparent.

2.3.6 Discussion on Non-clinical aspects

Pharmacology

Plenadren modified-release tablets contain hydrocortisone, which is a synthetic but structurally identical counterpart to cortisol. The pharmacological effects of hydrocortisone in man are both well-known and well described in the literature e.g. metabolic actions on carbohydrates, proteins and fat as well as anti-inflammatory and immunosuppressive actions and effects on brain function. Serum cortisol levels are highly and tightly regulated by the hypothalamic pituitary adrenal axis. Excess and deficient cortisol production and serum cortisol levels in man lead to diseases with significantly increase morbidity and mortality.

Hydrocortisone has been on the market for several decades and thus the clinical pharmacological experience with hydrocortisone is extensive.

Hydrocortisone (Plenadren) is designed to achieve once-daily morning dosing to deliver a physiological serum cortisol exposure. The systemic exposure to cortisol is therefore aimed at mimicking normal physiological levels of the hormone over time. The expected risk for exaggerated pharmacological effects is low.

No non-clinical pharmacological studies have been performed with Hydrocortisone (Plenadren) modified-release tablets. However, hydrocortisone is a well-known glucocorticoid and the synthetic form of the endogenously produced cortisol, so this is acceptable.

Pharmacokinetics

There is limited information on the absorption, distribution, metabolism and excretion of hydrocortisone in animals in the published literature. In rats, it has been reported that the fraction of the dose absorbed from the intestine is 93% and the intestinal permeability is high. There is a high correlation between humans and rats regarding intestinal permeability.

Following intravenous bolus injection the plasma concentration-time profile in rats followed a typical two compartment model, which is similar as in humans. The distribution phase was very rapid as the distribution half-life was about 8 minutes. The volume of distribution at steady-state (V_{ss}) was 1.24 ± 1.1 l/kg. This complies with a corresponding value in humans that was about 0.5 l/kg. In the same study; it was found that the central volume of distribution was 0.57 ± 12 l/kg and the terminal half-life 1.28 ± 1.6 hr. The total clearance (based on plasma concentrations) was about ten times higher than in humans, about 40 ml/min/kg compared to between 3-4 ml/min/kg.

After administration of ^{14}C -hydrocortisone, intramuscularly, sublingually and intragastrically to male rats more than half of the total radioactivity given was recovered in the faeces and the remainder in the urine. The rate of excretion was greatest after intravenous administration and decreased in order with sublingual, intramuscular and intragastric routes of administration. However, the amounts eliminated via the bile, urine and faeces were independent of the route of administration.

In conclusion, the clearance, volume of distribution and terminal half-life agreed fairly well between rats and humans.

A study in the dog showed that hydrocortisone is mainly metabolised in the liver, gastrointestinal tract and kidneys.

In pregnant mice, whole body radiography demonstrated that hydrocortisone passes over to the foetuses. The radioactivity in foetuses was however less than that in most maternal tissues.

Endogenous cortisol is excreted in small amounts in the breast milk in a circadian variation similar to that of plasma. Therefore it is reasonable to assume that hydrocortisone is excreted in human milk. This is reflected in SmPC section 4.6 Pregnancy and lactation.

Toxicology

There is limited information in the published literature on the general toxicity of hydrocortisone in animal studies. Data are old, sparse, not performed according to current guidelines and includes no details or references. The results report no unexpected toxicity findings. The data indicate that the acute toxicity is low after a 7-day observation period, but the mortality increases during the second week, presumably related to the immunosuppressive effects of the compound. A repeat-dose study in the rabbit induced hepatotoxicity, a well-known effect by high doses of glucocorticosteroids.

The only genotoxicity data available would indicate that hydrocortisone is not a mutagen, but has a clastogenic potential. The study is old, not performed according to present guidelines, the purity of the compound is not known and the GLP-status unknown. The results of the study are also in conflict with other published data for other synthetic corticosteroids as well as the studies performed with hydrocortisone aceponate. These studies were performed according to GLP and performed according to current guidelines. In a life-span study in rats given hydrocortisone no signs of carcinogenicity were found.

The available reproductive toxicity data demonstrate the well-known fact that hydrocortisone in high doses, like other corticosteroids, has a teratogenic and embryotoxic potential in laboratory animals. In a prenatal study in pregnant rats, indications of hormonal disturbances in the adult offspring were seen.

A study in the mouse demonstrated that hydrocortisone crosses the placenta, which is also the case in humans.

These findings are reflected in the SmPC in sections 4.6 Pregnancy and lactation and 5.3 Preclinical safety data.

Impurities and excipients

In general, the specifications of the impurities comply with the specifications in Ph.Eur. for hydrocortisone with the additional specifications listed in the Certificate of Suitability, R0-CEP 2002-220-Rev 03. However, the specification of Impurity G (hydrocortisone 21-aldehyde) is $\leq 0.4\%$ at release and $\leq 0.5\%$ at the end of shelf-life. Impurity G is included in the specifications in Ph.Eur. at $\leq 0.4\%$. Since hydrocortisone is marketed at doses up to 200 mg for other indications, this slight increase would have no toxicological importance. The residual solvents comply with the ICH-guidelines.

The pharmaceutical excipients are well known and commonly used in the pharmaceutical industry and fulfil the requirements of Ph.Eur.

Ecotoxicity/environmental risk assessment

The calculated EMEA Phase I PECsurfacewater ($0.00662\mu\text{g/l}$) is below the EMEA action limit of $0.01\mu\text{g/l}$. No other environmental concerns are apparent.

2.3.7 Conclusion on the non-clinical aspects

There is limited information in the published literature on the toxicological properties of hydrocortisone in animal studies. The results report no unexpected toxicity findings but may not form a complete basis for judgments on safety and efficacy, which is more appropriately made from the wide human clinical experience. Hydrocortisone is the pharmaceutical form of the endogenous glucocorticoid, cortisol. It has been used clinically for decades and the overall knowledge of its pharmaco-toxicological properties in humans is extensive. Hydrocortisone (Plenadren) modified-release tablet is for treatment of adrenal insufficiency and the peak systemic levels obtained is within the normal levels of cortisol in healthy humans.

Taking into account both the non-clinical literature available and the wide clinical experience of hydrocortisone, the CHMP is of the view that there is a sufficient basis to assess the safety of this product.

2.4 Clinical Aspects

2.4.1 Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

Table 1. Description of clinical studies

Study ID, study start, No. of patients	Design, control type, study and control drugs, dose, route and regimen	Study objectives	Diagnosis, inclusion criteria, gender (M/F) and median age (range)	Primary endpoint(s)
<p>DC 06/01</p> <p>FPI: Aug 2006</p> <p>LPO: Oct 2006</p> <p>Planned: 16</p> <p>Enrolled: 16</p> <p>Completed: 14</p>	<p>Single-centre, randomised, 2-way crossover, single dose study with an open food-interaction arm.</p> <p>Hydrocortisone (modified-release) oral tablet, 20 mg and 5 mg.</p> <p><u>5 mg and 20 mg study</u> -5 mg single dose (p.o.) fasting state -20 mg single dose (p.o.) fasting state</p> <p><u>Food interaction study</u> -20 mg single dose (p.o.) fed state</p>	<p>Single-dose PK and dose-proportionality of modified-release hydrocortisone in healthy volunteers.</p>	<p>-Healthy men and women aged 18-65 years. -BMI between 18 and 27 kg/m².</p> <p>M/F: 9/7 25.7 years (20-32)</p>	<p>PK variables (AUC, C_{max}, T_{max} and t_{1/2} with regard to dose proportionality)</p>
<p>DC 06/02 Part A and Part B</p> <p>FPI Part A: Aug 2007</p> <p>LPO Part A: Jul 2008</p> <p>FPI Part B: Mar 2008</p> <p>LPO Part B: Jan 2009</p> <p>Planned: 56</p> <p>Enrolled: 64</p> <p>Completed: 64</p>	<p>A randomised, controlled, open, two-armed, two-period (3 months each) cross-over, multi-centre phase II/III study (Part A) with a 6-month open extension (Part B). A pre-entry period of 4 weeks preceded the two-period (3 months each) cross-over followed by a 6-month open extension.</p> <p><u>Study drug:</u> Hydrocortisone (modified-release) oral tablet, 20 mg and 5 mg, administered o.d. 20-40 mg daily, individually adjusted.</p> <p><u>Control drug:</u> Hydrocortisone oral tablet. 20-40 mg daily, individually adjusted, administered t.i.d.</p>	<p>-To compare bioavailability between a modified-release o.d. hydrocortisone oral tablet and a conventional t.i.d. replacement therapy in patients with chronic primary AI. -To compare safety, tolerability and efficacy of the o.d. and t.i.d. therapy. -To assess the safety of the o.d. formulation as "rescue therapy" during minor intercurrent illnesses. -To assess long-term safety, tolerability and efficacy.</p>	<p>- Previously diagnosed (> 6 months ago) primary AI with a stable daily GC substitution dose for at least 3 months prior to study entry -Males and females ≥18 years - An oral hydrocortisone substitution therapy total daily dose of 20, 25, 30 or 40 mg.</p> <p>M/F: 37/27 45 years (19-71)</p>	<p>Difference in total serum cortisol AUC_{0-24h} between the novel modified-release treatment and conventional t.i.d. GC replacement therapy in all patients.</p>
<p>DC 08/01</p> <p>FPI: Oct 2008</p> <p>LPO: Ongoing</p> <p>Enrolled: 71</p> <p>67 patients completed 18 months.</p>	<p>An open, multi-centre, phase III, long-term follow-up study. This study will be ongoing as long as there is need for the enrolled patients to receive the o.d. modified-release formulation.</p> <p><u>Study drug:</u> Hydrocortisone (modified-release) oral tablet, 20 mg</p>	<p>Long-term safety, tolerability and efficacy of the o.d. treatment.</p>	<p>- Males and females ≥18 years - Previously diagnosed (> 6 months ago) primary AI with a stable daily GC substitution dose for ≥ 3 months - An oral hydrocortisone substitution therapy total daily dose of 15 to 40 mg.</p>	<p>Not defined.</p>

Study ID, study start, No. of patients	Design, control type, study and control drugs, dose, route and regimen	Study objectives	Diagnosis, inclusion criteria, gender (M/F) and median age (range)	Primary endpoint(s)
	and 5 mg, administered o.d. 20-40 mg daily, individually adjusted. Control drug: N.A.		M/F: 36/35 47 years (20-72)	

FPI: first patient in; LPO: last patient out; GC: glucocorticoid

2.4.2 Pharmacokinetics

Introduction

From a pharmacokinetic perspective the characteristics of the new modified-release product should be studied (rate and extent of absorption, fluctuations, dose proportionality, variability arising from the formulation, factors influencing the performance, and risk of unexpected release). The marketed immediate release product of the same active substance should serve as reference product. The relevant CHMP guideline states that if the drug exhibits non-linear pharmacokinetics it is necessary to compare the modified-release formulation and the immediate release formulation at the highest and the lowest dose following multiple dose administration. In addition in all cases dose proportionality for different strengths of the modified-release formulation should be adequately addressed.

The Applicant has not supplied all the above information. Furthermore, the data available is not of optimal quality as immunoassays have been used which shows ca 30% interference, probably from metabolites, and a LC-MS method has been used for which the validation data submitted is incomplete. The immunoassays used are commercially available assays which are used in clinical practice for analysis of cortisol. However, none of the methods have been properly validated according to available guidelines regarding bioanalysis for drug substances in clinical studies. The CHMP is, however, of the opinion that even if the analytical part of the PK dossier is not in line with today's standards for drug applications, within-study or within-subject comparisons may be considered sufficiently reliable for the general PK characterisation of the formulation, as it may be assumed that the known and potential errors are likely to affect the sample analysis of the two treatments compared in a similar way. However, there is an uncertainty regarding the comparison to physiological levels due to unknown possible differences in the immunoassay used in publications describing the physiological concentration time profile and the immunoassay used in study DC 06/02.

The dosing regimen applied for is once daily doses individualised according to the patients needs. Doses in the range 20 to 40 mg daily were used in patients with adrenal insufficiency (DC06/02). In case of intercurrent illness, dosing bid or tid (with 8 ± 2 hours between administrations) is proposed.

Analytical methods

Three analytical methods were used, an LC-MS/MS method specific for cortisol and two different immunoassays (Modular Analytics E, and Centaur). Both the LC-MS/MS method and an immunoassay method (Modular Analytics E) were used for the study in healthy volunteers (DC 06/01). The other immunoassay method (Centaur) was used for the study in patients (DC06/02).

In the validation for the LC/MS/MS method selectivity, linearity, precision, accuracy and stability was shown. In the calibration range 19.2-498 ng/ml plasma could be used as blank matrix for the calibration curve. However, at concentrations below 19 ng/ml endogenous cortisol interfered and MilliQ water was used as blank matrix in the calibration range 1.0-19.2 ng/ml. QCs for determination of precision and accuracy was 1.0 (water matrix), 96 and 498 ng/ml, and for stability evaluation 1.0

(water matrix) and 498 ng/ml (plasma matrix). No information regarding within study validation (i.e. data on method performance during analysis of study samples) was provided.

The immunoassays used are commercially available assays which are used in clinical practice for analysis of cortisol. The methods were validated by the manufacturers (Siemens and Roche, respectively) and are stated to be accredited according to SS-EN-ISO17025 and SS-EN-ISO15189 by SWEDAC. Acceptable precision has been demonstrated. However, the methods are not selective for cortisol; there is cross-reactivity of various endogenous steroids and synthetic steroids. The concentrations obtained with the Modular Analytics E immunoassay were 40-50% higher compared to the LC-MS/MS method. Long-term storage stability was claimed to be shown based on serum from blood donors stored at -20 °C for 10 months, which did not show any trend for decreased cortisol levels determined by the immunological assay. Control samples have been analysed the same day as study samples, in accordance with clinical practice and manufacturer's instructions, however QC samples have not been included in the actual study sample analysis runs as expected for bioanalysis for drug substances in clinical studies.

The Applicant has shown that the ratio of the difference between the bioanalysis methods Modular Analytics E vs LC-MS/MS seems to be stable over a dosing interval of 24 hours, covering a wide concentration range. A comparison between the Modular E and the Centaur immunoassays suggested a slightly lower level of interference with the Centaur assay (5%) but a good correlation between the methods over a wide concentration range (0-1000nM). Hence, as the level of interference does not change over time and given the good correlation between the two immunoassays both the LC-MS/MS assay and the immunoassays can be used to illustrate the shape of the concentration time profile, but there is an upwards shift of the concentration time profile with the immunoassay compared to the LC-MS/MS method.

Comparisons between the conventional tablets and Plenadren.

The concentration-time profile of Plenadren q.d. and conventional hydrocortisone t.i.d. was compared in [study DC06/02](#) in patients with adrenal insufficiency. The study was of sequential crossover design where patients were treated with total daily hydrocortisone tablet doses of 20, 25, 30 or 40 mg, doses being individually titrated based on clinical response. The total daily dose was divided and given (t.i.d. separated by 4 hours) as follows: 20 mg (10+5+5), 25 mg (15+5+5), 30 mg (15+10+5) or 40 mg (20+10+10). The patients were then switched to the same daily dose as Plenadren. As there is little accumulation of cortisol during multiple-dose administration, the pharmacokinetic data obtained may be seen as comparative to single dose data for Plenadren. Frequent blood samples were collected over 24 h. The results are presented below (Figure 2 exemplifies the plasma concentration time courses, table 2 presents the results irrespective of daily dose). When all dose levels were analysed together, the AUC_{0-24h} was about 20% lower (ratio 0.806 [95%CI: 0.753; 0.862]) after administration of prolonged release tablets than after conventional tablets.

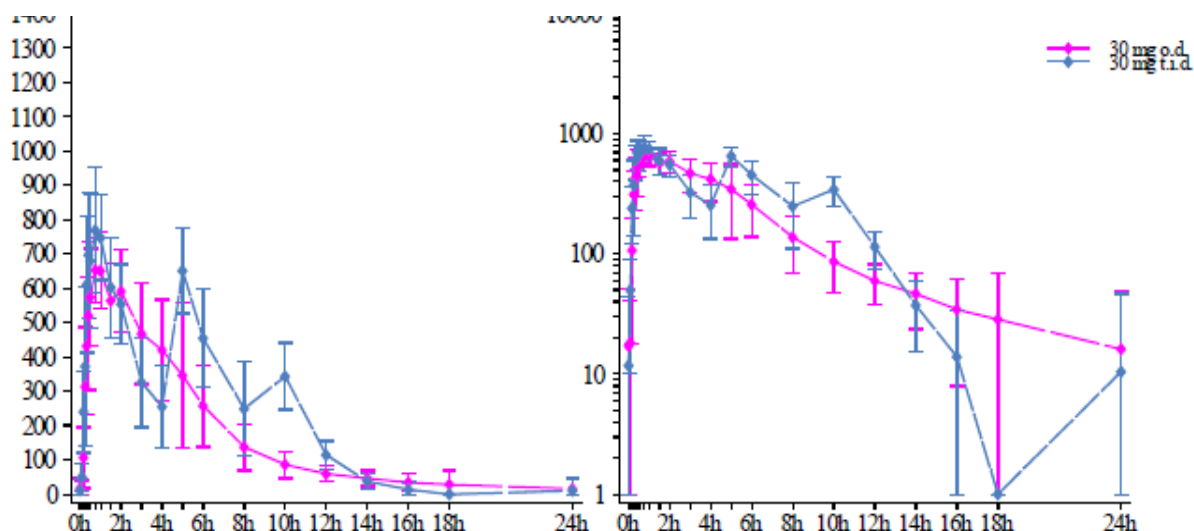


Figure 2. Mean (+/-SD) plasma concentration versus time after dosing of o.d. and t.i.d. after single+multiple dosage of 30 mg (Arm I+II), (ITT analysis set)

Table 2 Descriptive statistics and test for the primary PK variable, o.d. vs. t.i.d., at multiple dosage (Combined arm I+II) – ITT population with both o.d. and t.i.d.

		AUC ₀₋₂₄ (h x nmol/l)		
o.d.	t.i.d.	Difference o.d.-t.i.d. unadjusted mean (SD) median (range)	Quotient o.d./t.i.d. or difference o.d.-t.i.d. period-adjusted (95% CI)	p-value ^a o.d.-t.i.d. period- adjusted
mean (SD) median (range)	mean (SD) median (range)			
3962.0 (1079.6) 3928.5 (1789.4; 7346.5) n=59	4879.6 (1194.4) 4839.2 (2742.2; 7621.4) n=59	-917.6 (1114.5) -935.2 (-3936.7; 1632.3) n=59	Quotient: 0.806 (0.753-0.862)	<.0001

^a GLM on the logarithms was used to compare differences period 1 – period 2 between patients with o.d. first period and patients with t.i.d. first period.

The blood samples of this study were analysed by an immunoassay (Centaur) for which the validation data is sparse and mainly derived from the manufacturers documentation. However, if assuming that during the analysis of these samples, the potential errors will have affected the analysis results in a similar way for the two treatments, the comparison of treatments is considered sufficiently reliable for comparison of the shape of concentration time profile and relative PK parameters for Plenadren q.d. vs IR t.i.d.

Dose proportionality – between strengths and dose levels

As different doses and dose regimens will be used, the dose proportionality of the two strengths needs to be evaluated and a comparison of whether the dose-exposure relationship is similar for the different formulations supplies useful background information for changing from treatment with conventional tablets to Plenadren.

There are two sets of dose proportionality information. The first is the proportionality of exposure between the two different Plenadren strengths. This has been investigated in a study in healthy volunteers (DC06/01) with pharmacologically induced suppression of the endogenous cortisol production. In this study, single doses of 5 and 20 mg Plenadren were compared during fasting

conditions. (There was also a fed condition part discussed separately below.) In this study it was shown, that instead of the expected 4-fold difference in exposure between strengths, the increase in exposure (AUC) when comparing 20 to 5 mg was 3-fold. Thus, the exposure is increased when increasing the strength, but is not completely dose-proportional. The reasons for this are unknown but as nonlinear pharmacokinetics of cortisol has been reported, potentially caused by saturable protein binding or dose dependent bioavailability due to incomplete dissolution, this may be a substance and not a formulation effect. LC-MS/MS was used for quantification of cortisol in plasma in this study. This method does not have interference but has not been validated in an optimal way. However, the results may be used to illustrate relationship in total cortisol exposure between the two strengths.

The second part of the dose-proportionality documentation is related to dose proportionality in the therapeutic dose range. As doses as high as 40 mg qd may be administered in patients in the normal treatment situation without intercurrent illness, it is adequate to show that the differences in drug release pattern between the conventional tablet and Plenadren does not give rise to any major differences in the dose-exposure relationship. In study DC06/02 where patients were transferred from conventional tablets tid to Plenadren qd, full concentration-time profiles are available for different daily doses. The mean (SD) AUC(0-24h) for conventional tablets t.i.d. was 4305 (1285), 5353 (1256), 4905 (1155) and 4770 (1140) nmol*h/l at the total daily dose levels 20 (n=8), 25 (n=4), 30 (n=36) and 40 mg (n=13), respectively. The corresponding values for Plenadren were 3250 (998), 4290 (278), 3757 (956) and 4357 (1179) nmol*h/l, respectively. For the different dose levels in the study the AUC-ratios [95%CI] q.d./t.i.d.were as follows: 0.737 [0.596; 0.912] N=8 for the 20 mg dose, 0.784[0.371;1.658] N=4 for 25mg dose, 0.762[0.710; 0.818] N=36 for the 30 mg dose and 0.911[0.821;1.011] N=13 for the 40 mg dose. Since the number of subjects on some dose levels were small, the precision in the estimates are poor and an approximate 20% difference may be concluded supporting the fact that the relationship between dose and AUC is similar for the two formulations. The AUC observed per dose level was not proportional to dose for any of the formulations, with AUCs of the same magnitude at the 25, 30 and 40 mg dose levels. There may be several contributing factors to this observation including a higher clearance in patients with a higher dose requirement, reduced bioavailability at higher doses and possibly saturable protein binding. These data were obtained with a non-specific immunoassay method. However, under the assumption that the interference is similar for both products, inter formulation comparison of concentration-time profiles and by calculating the AUC ratio can be made.

In intercurrent illness, dosing bid or, if needed, tid, with Plenadren is recommended using 8-hour intervals between administrations. Since the same dose per occasion is given but in a higher frequency, the resulting exposure in the patient with intercurrent illness may be estimated by calculations using the superposition principle and is expected to increase in proportion to dose.

Rate of absorption and the effect of food

The time to reach a clinically significant plasma concentration of cortisol in the morning (>200 nmol/l) was less than 30 minutes in the fasted state after a 20 mg dose (DC06/01).

Plenadren is recommended to be administered under fasting conditions. However, during the dosing regimen proposed during intercurrent illness (bid or tid regimen) it will be impossible to maintain fasting conditions. The effect of food was studied for the highest strength (20 mg) under single dose conditions (DC06/01). A high fat meal affected the rate and extent of absorption. AUC increased by about 30%. Mean baseline corrected values are shown in Figure 3. LC-MS analysis was used in this study.

Study: DuoCort
Mean over time points for Corrected Pharmacokinetic values
ITT population

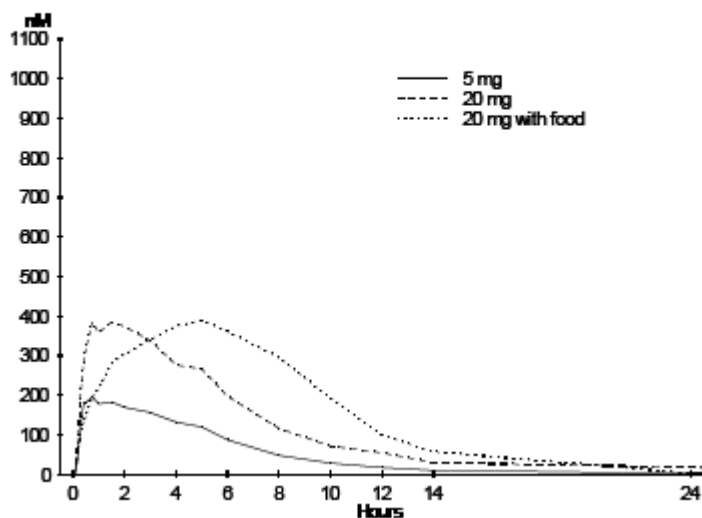


Figure 3 Mean plasma concentration-time profile for hydrocortisone for corrected plasma data ITT population

Population PK analysis

The main purpose of this analysis was to describe the cortisol population pharmacokinetics (POPPK) after different Plenadren doses in patients and healthy volunteers with suppressed endogenous cortisol production. Based on the final POPPK model, simulations were made for dosing recommendations in intercurrent illness situations. In addition, nomograms based on body weight and serum cortisol concentrations were initially derived in order to provide tools for individualised dosing. The POPPK of cortisol after different doses of hydrocortisone tablets in patients was also described.

Plasma cortisol concentration time data from studies DC 06/01 and DC 06/02 were included in the analysis. Only data from the fasted condition was used from the Phase I study (DC 06/01). In total, 75 individuals (1713 observations) contributed to the POPPK analysis.

The final POPPK Plenadren model consisted of a 2-compartmental model with first order absorption with a lag-time and including a linear increase in oral clearance (CL/F) with increasing weight. This formed the basis for the initially proposed weight nomogram. A nonlinear relationship in bioavailability (F) with increasing dose was described and the bioavailability was predicted to be 36% lower after 40 mg compared to 20 mg Plenadren. Oral clearance was estimated to be 17% lower and volume of distribution in the central compartment 30% lower in healthy subjects. A constant baseline shift in hydrocortisone profiles during the 24hour dosing interval was applied. Baseline levels were estimated to be 39.8 nM and 19.2 nM in patients and healthy volunteers respectively. A separate POPPK model for hydrocortisone tablet t.i.d. administration was also developed in order to compare the exposure between conventional hydrocortisone tablet and Plenadren in relation to a normal circadian cortisol profile.

The population PK model describes the observed data well and predicts the observed plasma concentrations well. However, as the data used for the analysis is from immunoassays, the use of the model has limitations. As interference has been observed, probably by metabolites, and as there may be a relation between clearance (proposed to be affected by bodyweight) and degree of formation of interfering metabolites, the covariate relationship may be uncertain. Moreover, it cannot be excluded that part of the difference between healthy subjects and patients in estimated pharmacokinetics

parameters is related to the different immunoassays used. The non-proportional increase in exposure with increased dose has been modelled as a decrease in bioavailability with increased dose. However, given the study design with titration of doses based on clinical response and the resulting similar exposure at the 25, 30 and 40 mg dose levels, it seems likely that patients with higher oral clearance have been titrated to higher dose levels. Consequently, the model may not describe the actual increase in proportion to dose due to the limitation of the study design. Hence, these data cannot be used to evaluate dose proportionality of Plenadren.

Literature data supporting the pharmacokinetics of cortisol

Literature data on the pharmacokinetics and pharmacodynamics of hydrocortisone has been provided. Hydrocortisone is rapidly and well absorbed from the gastrointestinal tract, bioavailability 96% for an oral 20 mg dose (Derendorf et al 1991). This figure has been estimated with a radioimmunoassay method which is most likely not selective for cortisol and hence should not be interpreted as absolute bioavailability since metabolites are most likely measured as well as cortisol. The dissolution rate *in vivo* is reduced at higher oral doses, which has been reported as a less than proportional increase in plasma exposure with increasing oral dose of hydrocortisone even when the drug is given orally as a suspension in the dose range 5-40 mg (Toothaker et al 1982a; Toothaker et al 1982c). In the first study referred to tablets in doses of 10, 30 and 50 mg were used and in the second study IV doses were administered. In these studies capacity limited protein binding is discussed as a possible contributing factor.

The PK parameters of cortisol after intravenous single bolus dose administration of hydrocortisone (hydrocortisone sodium succinate) as 5, 10, 20 and 40 mg given to dexamethasone suppressed healthy male subjects (n=6) have been investigated using a HPLC-UV method. The terminal half-life for each of the four doses was 1.3, 1.3, 1.7 and 1.9 hours, respectively. The clearance and volume of distribution were 120, 125, 137 and 169 ml/min, respectively and 21, 21, 26 and 38 L, respectively, for these four intravenous doses (Toothaker et al 1982c). At concentrations below 200 ng/ml (500 nM), plasma hydrocortisone is tightly bound to transcortin, and the free fraction of circulating drug is only 5 %. At plasma hydrocortisone concentrations greater than 200 ng/ml, a greater proportion of compound is loosely bound to albumin, and the free fraction increases to approximately 25 % (Toothaker et al 1982c). The data referred to suggests that drug concentration-dependent changes in the binding of hydrocortisone may explain the apparent increase in V_{dss} and increasing total clearance with increasing intravenous doses.

The terminal half-life has been reported to be about 1.5 hours following intravenous (IV) and oral immediate release dosing of hydrocortisone. The terminal half-life of endogenously secreted cortisol in plasma/serum is longer (3 to 5 hours) due to an ongoing pulsative secretion that follows a specific circadian pattern. This is due to the fact that the PK of endogenous cortisol is secretion-controlled rather than elimination-controlled. Hydrocortisone is a small and lipophilic drug (clog P 1.6; MW 362.5), which is eliminated completely through metabolism by 11 β HSD type 1 and type 2 enzymes and CYP 3A4 in the liver and peripheral tissue. CYP 3A4 is involved in the clearance of hydrocortisone by the formation of 6 β -hydroxycortisol, which is excreted in urine (Czock et al 2005). Cortisol is metabolised to the inactive metabolite cortisone and further to dihydrocortisone tetrahydrocortisol and 5 α -tetrahydrocortisol. Hydrocortisone has been shown to have affinity and to be transported by P-glycoprotein (MDR1/ABCB1) (Ueda et al 1992; Karssen et al 2001, Faassen et al 2003; Yates et al 2003).

Drug-drug interactions mediated by cellular transport proteins are unlikely due to the high permeability. Renal and biliary clearances of unchanged hydrocortisone contribute negligibly to the total clearance (Czock et al 2005). Drugs may affect cortisol clearance by inducing or inhibiting the various enzymes involved in the metabolism of cortisol, such as CYP 3A4 and other specific steroid

enzymes. Potent CYP 3A4 inducers can enhance the metabolic clearance of cortisol, decrease terminal half-life and thus reduce circulating levels and increase fluctuations of cortisol. This may require dose adjustment of hydrocortisone. Potent CYP 3A4 inhibitors can inhibit the metabolism of hydrocortisone, and thus increase blood levels. The effect of corticosteroids may be reduced for 3-4 days after interaction with mifepristone.

2.4.3 Pharmacodynamics

No new data on the pharmacodynamics of hydrocortisone have been provided by the Applicant; instead a brief summary based on published review was submitted as follows. Considering that hydrocortisone is a well-known and well-characterised substance, this is acceptable.

The endogenous glucocorticoid cortisol has widespread actions on metabolism and the functioning of various organs (Axelrod 2006). Endogenously produced and secreted cortisol regulates glucose and substrate metabolism, participates in the fine-tuning of the immune system through an endocrine-immune feed-back loop (Chrousos 1995), regulates vascular tonus and influences brain function. Excess glucocorticoid exposure such as during a Cushing's syndrome or during pharmacological glucocorticoids therapy is therefore associated with increased risk of DM, adiposity, muscle and skin atrophy, osteoporosis, suppression of the immune response and impaired cognitive function. On the other hand, in glucocorticoid deficiency, a stressful event such as a minor infection can lead to an acute life-threatening situation with high fever leading to shock and death within hours if not treated adequately.

2.4.4 Discussion on clinical pharmacology

One of the main deficiencies in this application is the analytical methods used. None of the bioanalysis methods applied, immunoassay and LC-MS/MS, have been validated according to current guidelines regarding bioanalysis for drug substances in clinical studies. Considering the claimed importance of the pharmacokinetic profile, bioanalysis of all samples by a fully validated, selective chromatographic method such as LC-MS/MS would have been expected. The available validation data for the LC/MS/MS method suggest acceptable selectivity, precision, accuracy and stability. The validation was however based on lower number of QCs than recommended in current guidelines. Moreover, within-study validation (i.e. data on method performance during analysis of study samples) has not been provided. Accuracy and precision during sample analysis has thus not been confirmed. The CHMP is of the opinion that despite the uncertainty regarding accuracy and precision during sample analysis it is acceptable to use the PK data for a within-study general characterization of the formulation as a potential error can be assumed to be the same for the two strengths. The obtained data describing dose proportionality between 5 and 20 mg, and food effect, can therefore be considered sufficiently reliable. The data can also be used to illustrate the shape of the concentration-time profile.

Although the immunoassays used are commercially available assays, validated by the manufacturers, and which are used in clinical practice for analysis of cortisol, the validation does not comply with the recommendations in current guideline documents regarding bioanalysis for drug substances in clinical studies. The methods are not selective for cortisol. The concentrations obtained with the Modular Analytics E immunoassay were 40-50% higher compared to the LC-MS/MS method. The ratio between the concentrations determined with the two methods was however stable over the 24 hour dosing interval covering a wide concentration range. There is hence, an upwards shift of the concentration time profile with the immunoassay. However, the shape of the concentration-time profile remains the same. Data on long term storage stability is based on serum from blood donors stored at -20 °C for 10 months. However, as the immunoassay is non-specific it cannot be excluded that there may be a breakdown of cortisol over time and that other components interfering with the immunoassay is

formed (i.e. resulting in a similar amount of cortisol and interfering substances but with decreasing concentrations of cortisol and increasing concentrations of interfering substances over time). Hence, reliable data is lacking to support stability of cortisol at storage of -20 °C (or -70 °C) over 10 months as used in study DC06/02. The CHMP is of the opinion that despite insufficient accuracy and selectivity of the method it is considered acceptable to use the PK data for a within-study or within-subject general characterization of the two formulations as the error can be assumed to be the same for the two formulations as long as clearance is unaffected. However, use of data obtained with immunoassay for covariate evaluation in the population analysis is not adequate as with interference from metabolites, there may be a covariation between degree of interference and clearance (metabolite formation) leading to an incorrect estimation of the effects of covariates in the analysis. Comparison of measured concentrations to published data for the cortisol profile in healthy volunteers, should also be made with caution, as the two immunoassays may differ in degree of non-specificity making this comparison of absolute values uncertain.

Available LC-MS/MS data shows that the two Plenadren strengths do not give a dose proportional response. A 3-fold increase is obtained when comparing the AUC obtained with 20 mg to the 5 mg strength. Study 06/02 suggests that exposure will be 20% lower after a switch from the conventional tablet to Plenadren on a mg daily basis. Under the assumption that the formation of interfering metabolites is similar for the two products, it may also be concluded that the degree of nonlinearity in AUC (related to absorption) when increasing the dose administered on one occasion appears similar between formulations.

In clinical practice the dose is titrated based on clinical response without any measurement of cortisol levels. The CHMP is therefore of the opinion that the pharmacokinetic data are sufficiently reliable for characterisation of dose proportionality 5 vs 20 mg, food effect and comparison of shape of concentration time profile and relative PK parameters for Plenadren q.d. vs IR t.i.d.

Study DC 06/02 was of sequential crossover design where patients were treated with total daily hydrocortisone tablet doses of 20-40 mg, doses being individually titrated based on clinical response. An immunoassay was used, which is not selective for cortisol. AUC was similar at dose levels 25, 30 and 40 mg, which may be caused by patients with higher oral clearance being titrated to higher doses. As oral clearance is likely to be different in the different dose groups, this study cannot be used for evaluation of dose proportionality per se or for the evaluation of bioavailability at different dose levels. However, as each patient was treated with both Plenadren and the approved conventional tablet, the results can be used to detect differences in dose proportionality between products if such would exist. A similar exposure ratio between the two treatments was obtained at the different dose level indicating that the dose proportionality in the dose range 20-40 mg/day is similar for the two products.

The population PK analysis predicts the observed plasma concentrations well (representing the mixture of cortisol and interfering substances as the data have been obtained by immunoassay). Hence, simulations of concentration time profile after increasing the dosing frequency to twice or thrice daily dosing in intercurrent illness can reliably be made using this model. However, as there may be a covariation between degree of interference and individual clearance (metabolite formation) and the risk of erroneously estimated dose dependency in bioavailability due to the design of the study (titrated doses) the model cannot be used to support the initially suggested weight and PK nomograms for dose adjustments. For the same reason there are uncertainties in the simulated concentration-time profiles of increased doses of IR t.i.d in intercurrent illness.

2.4.5 Conclusions on clinical pharmacology

None of the bioanalysis methods applied, immunoassay and LC-MS/MS, have been fully validated according to current guidelines regarding bioanalysis of drug substances in clinical studies. The immunoassays used show ca 30% interference, probably from metabolites. Hence, the pharmacokinetic data must be interpreted with caution. However, the ratio of the results obtained with Modular Analytics E immunoassay compared to the LC-MS/MS method seems stable over the 24 hour dosing interval. The CHMP is therefore of the opinion that even if the analytical part of the PK dossier is not in line with today's standards for drug applications, within-study or within-subject comparisons may be considered sufficiently reliable for the general PK characterisation of the formulation, as it may be assumed that the known and potential errors are likely to affect the sample analysis of the two treatments compared in a similar way.

The pharmacokinetic data are considered sufficiently reliable for characterisation of dose proportionality 5 vs 20 mg, food effect and comparison of shape of concentration time profile and relative PK parameters for Plenadren q.d. vs IR t.i.d. In the dose range 20-40 mg the AUC ratio between Plenadren and conventional tablets was similar, indicating that the dose proportionality in the dose range 20-40 mg/day is similar for the two products. Hence, when changing treatment from conventional tablets to the same total daily dose of Plenadren there will be an approximately 20% decrease in overall exposure (AUC) regardless of dose level. Furthermore, although conclusions regarding covariate effects cannot be drawn from the population PK analysis (due to the use of a non-specific immunoassay and the study design limitations), the PopPK model described the observed data well and can therefore be used for simulations of increased dosing frequency of a certain dose (as the bioavailability remains constant). Hence, the simulations of the concentration time profile and daily exposure when increasing the total daily dose in intercurrent illness by administering Plenadren twice or thrice daily with 8h intervals is considered reliable. The PopPK model can also be used for simulations of the concentration-time profile and concentrations at certain time points for the doses studied. However, there is an uncertainty regarding the comparison to physiological levels due to unknown possible differences in the immunoassay used in publications describing the physiological concentration time profile and the immunoassay used in study DC 06/02.

2.4.6 Clinical efficacy

Dose-response studies and main clinical studies

No dose response study was submitted as part of this hybrid marketing authorisation application. Since the focus of the application is to compare the pharmacokinetics of Plenadren with conventional hydrocortisone treatment and further to show that the PK profile mimics the endogenous profile of cortisol, the lack of dose response studies is acceptable.

Pivotal Study DC 06/02

The main study evaluating efficacy and safety is DC 06/02 (part A). The open-label extension DC 06/02 (part B) is considered to be supportive. The study was conducted as an open, controlled, randomised, two-armed, two-period 12-week cross-over, multi-centre trial (part A) with an open controlled period of 6 months on the novel therapy with an optional open extension phase (part B). Five centres in Sweden participated in the study.

The primary objective of the study was to compare the bioavailability and pharmacokinetics of the modified-release tablet with the conventional therapy taken three times per day in patients with chronic primary adrenal insufficiency in terms of the difference in total serum cortisol (S-cortisol) AUC_{0-24h}.

Secondary clinical objectives were:

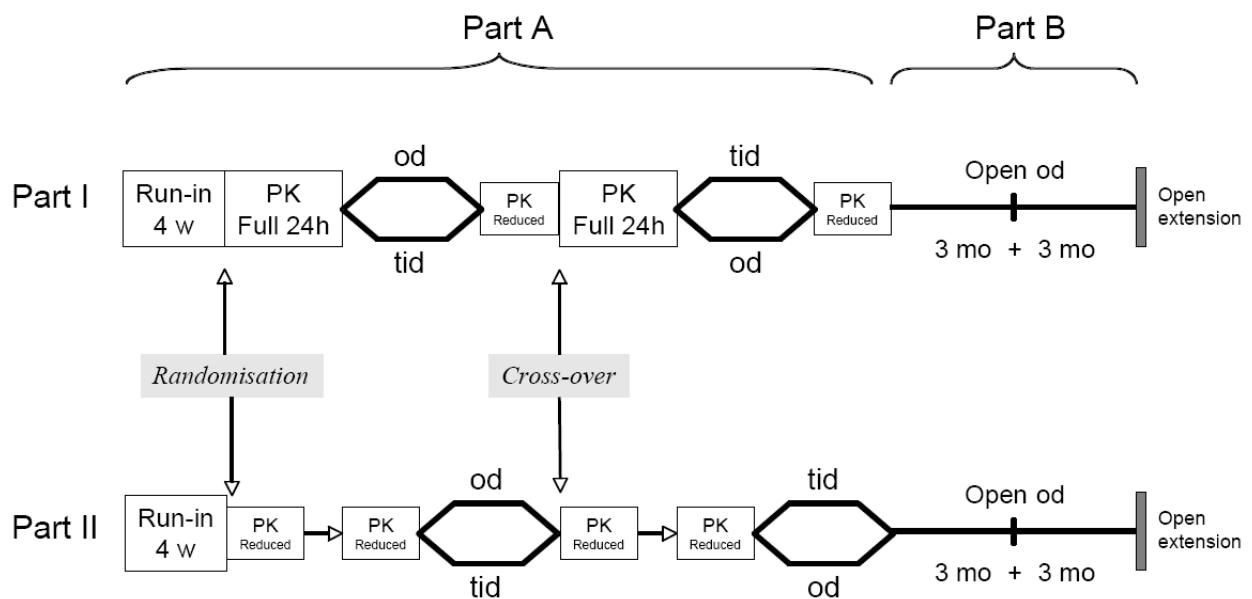
- to compare safety, tolerability and efficacy of the novel modified-release formulation to the conventional thrice-daily replacement therapy.
- to assess the safety of using the novel modified-release formulation as "rescue therapy" during minor intercurrent illnesses in patients with primary adrenal insufficiency.
- to assess long-term safety, tolerability and efficacy of the novel modified-release formulation during glucocorticoid replacement therapy.

The secondary clinical endpoints were:

- well-being, i.e. QoL assessed by three validated questionnaires (SF-36, FIS and PGWB);
- diurnal fatigue (VAS);
- patient preference as by questionnaire;
- patient tolerability as by questionnaire (patient and physician).

The study design is described in Figure 4 below. After a four week run-in period where all patients who were not already on t.i.d. treatment were switched to this regimen, patients were consecutively randomised to one of the following two treatment sequences AB and BA, where A is the test drug and B is the reference drug.

Figure 4 Overall study design visit arm I (part I) and arm II (part II)



Patients included into study arm I were all allocated to the one centre with facilities to perform full PK measurements, while all patients included into study arm II were allocated to the other participating centres.

After randomisation to conventional t.i.d. or novel once daily (o.d.) therapy patients in study arm I underwent standardised in-house pharmacokinetic (PK) sampling during 24 hours in order to assess single-dose PK of o.d. or t.i.d. regimen while patients in study arm II had a reduced PK sampling scheme of single dose PK on day 1-2 and returned for multiple-dose PK sampling on day 7-8. Irrespectively of dose at run-in, the original protocol stated that all patients were to receive 30 mg

cortisol on the PK sampling days according to the original study protocol. This was changed to individual dosing also on the PK sampling days in accordance with protocol amendment No. 1.

The patients continued with the assigned treatment for 12 weeks. The patients returned every 4 weeks for study drug dispensation, adverse event (AE) assessment and collection of patient questionnaires including three validated quality of life (QoL) tests (FIS, SF-36 and PGWB) and one non-validated diurnal fatigue score (visual analogue scale [VAS], morning, noon, afternoon). After the 12-week study period, patients were admitted for full clinical examination, laboratory sampling and other assessments including diurnal fatigue score and further reduced PK sampling for an initial 0-10 hours in-house and return for the 24 hours samples (i.e. for multiple-dose PK). After the cross-over to the other randomised treatment (t.i.d. or novel o.d. therapy), PK sampling was repeated.

The patients continued for another 12 weeks with the assigned second randomised treatment. After the 12-week study period, the patients were admitted for full clinical examination, laboratory sampling and other assessments, including diurnal fatigue score. Patients in study arm I had another reduced PK sampling (0-10 hours in-house and a return visit for the 24-hour samples), i.e. for multiple-dose PK.

After the second cross-over treatment period, the patients continued in a 6-month open extension on the novel o.d. therapy (DC 06/02, Part B).

The main inclusion and exclusion criteria were:

Inclusion Criteria

- Males and females; age 18 years and above;
- Previously diagnosed (e.g. more than 6 months ago) primary adrenal insufficiency with a stable daily glucocorticoid substitution dose for at least 3 months prior to study entry;
- An oral hydrocortisone substitution therapy dose of 20, 25, 30 or 40 mg total daily dose;
- Signed informed consent to participate in the study.

Exclusion Criteria

- Clinical or laboratory signs of significant cerebral, cardiovascular, respiratory, hepatobiliary, pancreatic disease, which in the investigator's judgment could interfere with the study assessment or completion of the study;
- Clinically significant renal dysfunction with a serum creatinine above 150 µmol/l;
- Clinical or laboratory signs of significant gastrointestinal emptying or motility disease or disorder including pharmacological therapies affecting gastrointestinal emptying or motility, which in the investigators judgment could interfere with the ADME (administration-distribution-metabolism-elimination) of hydrocortisone;
- Any medication with agents which could interfere with hydrocortisone kinetics within 14 days prior to study start;
- Any additional underlying disease that may need regular or periodic pharmacological treatment with glucocorticoids;
- Administration of other investigational drugs within 8 weeks preceding the pre-entry examination;
- Regular dehydroepiandrosterone (DHEA) medication for the past 4 weeks;

- Oral oestrogen medication for the past 4 weeks (transdermal oestrogen medication was allowed);
- Deranged mineralocorticoid status as determined by clinical (hypotension, ortostatic hypotension) and biochemical status (serum sodium and potassium levels).

Inclusion and exclusion criteria are generally acceptable. The SmPC reflects the lack of data in patients with conditions that affect gastrointestinal motility.

Treatments were as follows:

Test drug: hydrocortisone (modified-release), oral tablet, available as 20 mg and 5 mg.

The modified-release hydrocortisone tablet was administered orally o.d. at 8 AM in the fasting state. During the 12-week period of Part A and the 6-month period of Part B, the patient's daily dose of hydrocortisone was administered as follows:

<u>Daily dose at run-in</u>	<u>Hydrocortisone modified-release</u>
20 mg	20 + 0 + 0 mg
25 mg	(20 + 5) + 0 + 0 mg
30 mg	(20 + 5 + 5) + 0 + 0 mg
40 mg	(20 + 20) + 0 + 0 mg

Reference drug: hydrocortisone, oral tablet, 10 mg

The reference drug was administered orally thrice daily (at 8 AM, 12 AM and 4 PM). The morning dose was administered in the fasting state. During the run-in period, the 12-week period during Part A, the patient's daily dose of hydrocortisone was administered as follows:

<u>Daily dose at run-in</u>	<u>Reference drug t.i.d</u>
20 mg	10 + 5 + 5 mg
25 mg	15 + 5 + 5 mg
30 mg	15 + 10 + 5 mg
40 mg	20 + 10 + 10 mg

No adjustments of the maintenance dose were allowed during the study period.

No blinding took place during the trial. The Applicant's justification for this is that none of the primary objectives/variables and objective biochemical secondary objectives/variables and safety assessments are judged to be affected by a blinding procedure. Moreover, it was not considered ethical and safe to blind the trial as that would involve dummies that could cause patient's death in case of an intercurrent illness and/or acute adrenal crisis. This justification was accepted by the CHMP when this issue was discussed during the scientific advice procedure prior to the submission of the MAA. It was, however, noted that the QoL measurements and the safety assessment may be hampered by the open-label design. The chosen endpoints were in accordance with the CHMP scientific advice.

The statistical methodology applied in the clinical evaluation is adequate.

Results

Table 3 Disposition of patients

	o.d. n (%)	t.i.d. n (%)
Patients included in the study	64 (100.0%)	64 (100.0%)
Intent-to-treat Population	63 (98.4%)	63 (98.4%)
Per Protocol Population	55 (85.9%)	55 (85.9%)
Safety Population	64 (100.0%)	64 (100.0%)
Patients Completed the Study	64 (100.0%)	64 (100.0%)

The ITT population included 63 patients and the PP population included 55 patients. All 64 patients included received at least one dose of study medication and are included in the safety population. One patient who failed with regard to the multiple dose PK sampling was included in the safety population but not the ITT population. Except for the multiple dose PK sampling, this patient otherwise completed the study according to the protocol. The classification into the PP population was based on to what extent it was possible to correctly assess the primary efficacy variable, i.e. multiple dose AUC0-24h. All patients completed the study.

Five clinical centres in Sweden participated in the study. First patient was included in Aug 2007, last patient finalised the study in Jul 2008. The center performing the full PK measurements included 21 patients. Remaining patients were evenly distributed between centres.

Three amendments were made to the study protocol. The first amendment concerning the dose to be given at the day of the full PK-sampling could have affected the interpretation of the PK-data. The amendment, however, was made before the randomisation of the first patient. The statistical methods were changed in the third protocol amendment. The Applicant has provided reasons for the amendment and has also provided reassurance that that the changes were not influenced by knowledge of the data collected at the time of the amendment.

The demographic baseline data are presented in Table 4. The recruited patients are considered to be representative for patients with primary adrenal deficiency. The mean duration of disease was 16.9 (10.5) years.

The majority of patients (55 %) were using hydrocortisone b.i.d. at inclusion and the majority of patients had a daily dose of 30 mg (57 %). A rather large proportion (21 %) was diagnosed with diabetes. This is to be expected since these conditions share an autoimmune pathophysiology.

Table 4 Demographics and baseline characteristics - ITT and PP populations

Variable		ITT (n=63)	PP (n=55)
Age (years)		47.3 (13.7)	47.1 (13.8)
		45.8 (19.5; 71.5) n=63	44.0 (19.5; 71.5) n=55
Sex	Male	37 (58.7%)	34 (61.8%)
	Female	26 (41.3%)	21 (38.2%)
Weight (kg)		79.6 (14.3)	80.1 (14.6)
		79.4 (54.2; 121.1) n=63	80.6 (54.2; 121.1) n=55
Height (cm)		174.2 (8.4)	174.9 (8.4)
		176.0 (154.0; 193.0) n=63	176.0 (154.0; 193.0) n=55
BMI (kg/m ²)		26.2 (4.0)	26.1 (4.0)
		25.5 (18.6; 37.3) n=63	25.5 (18.6; 37.3) n=55
SBP (mm Hg)		123.6 (19.7)	123.5 (20.5)
		120.5 (74.0; 182.5) n=63	119.0 (74.0; 182.5) n=55
DBP (mm Hg)		75.8 (11.5)	75.5 (11.9)
		75.0 (47.5; 105.0) n=63	75.0 (47.5; 105.0) n=55
Heart rate (bpm)		65.5 (10.4)	64.9 (10.4)
		64.5 (47.5; 97.0) n=63	63.5 (47.5; 97.0) n=55
ECG	Normal	56 (88.9%)	50 (90.9%)
Tobacco use	Yes	11 (17.5%)	10 (18.2%)
Pregnancy test	Negative	16 (25.4%)	13 (23.6%)
	Male/Post menopause N/A	47 (74.6%)	42 (76.4%)
Current replacement dose (mg)	20 mg	8 (12.7%)	8 (14.5%)
	25 mg	6 (9.5%)	4 (7.3%)
	30 mg	36 (57.1%)	32 (58.2%)
	40 mg	13 (20.6%)	11 (20.0%)
Current replacement dose (tablets per day)	b.i.d.	33 (55.0%)	30 (56.6%)
	t.i.d.	27 (45.0%)	23 (43.4%)
Daily dose at run-in (mg)	20 mg	8 (12.7%)	8 (14.5%)
	25 mg	6 (9.5%)	4 (7.3%)
	30 mg	36 (57.1%)	32 (58.2%)
	40 mg	13 (20.6%)	11 (20.0%)
Diabetes		13 (20.6%)	12 (21.8%)
Hypertension		11 (17.5%)	11 (20.0%)

For categorical variables n (%) is presented. For continuous variables Mean (SD), Median (Min; Max) and n are presented.

Compliance was calculated as days during study period multiplied by the daily cortisol use yielding the expected cortisol consumption. The actual consumption was assessed by counting the actual tablets returned by the patient at each visit. The difference was divided by the expected cortisol consumption and expressed as percentage compliance.

According to the Applicant the difference in compliance observed within the treatment groups is probably due to the additional cortisol use, please see below and Table 5.

Since one of the reasons for developing a o.d. regimen is to improve compliance it is noteworthy that the compliance variation (range) was less during the periods with o.d. treatment.

Table 5 Compliance on o.d. and t.i.d. and the difference o.d. - t.i.d.

Variable	ITT (n=63)	
	Mean (SD) Median (Min; Max)	p-value within group
Compliance during o.d.	104.8 (7.5) 102.4 (94.7; 138.9) n=58	0.0420
Compliance during t.i.d.	103.1 (13.2) 100.9 (61.2; 168.2) n=58	
Difference in compliance o.d.-t.i.d.	1.28 (15.08) 2.26 (-63.47; 43.04) n=56	

For continuous variables Mean (SD) / Median (Min; Max) / n= are presented.
For comparison over time within groups Wilcoxon Signed Rank test was used.

Patient tolerability

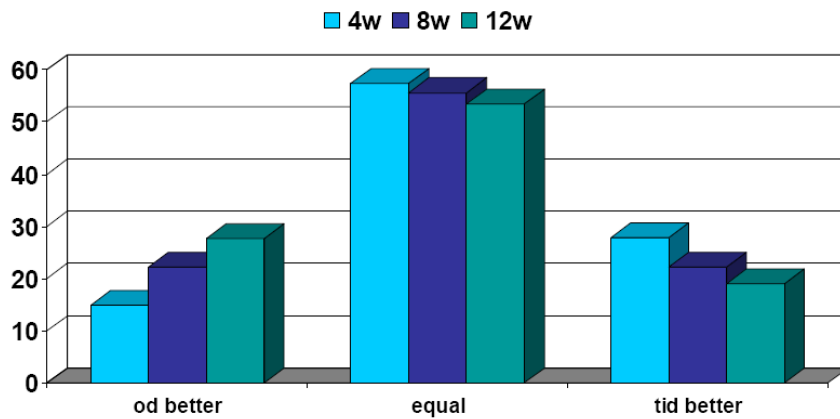
Tolerability was assessed in questionnaires by both the patient and the investigator. The proportion of patients assessing that they had been very well on treatment increased from 43.3% at baseline to 54.1% at 12 weeks on o.d. treatment and to 50.0% on t.i.d. treatment. The corresponding investigator assessment of patients tolerating the treatment very well increased from 41.7% at baseline to 51.8% at 12 weeks on o.d. and to 50.9% on t.i.d. treatment.

At baseline, none of the patients in the ITT population tolerated the treatment poorly as assessed by the patient or the investigator. At 12 weeks, one patient (1.6%) on o.d. treatment vs. none on t.i.d. treatment answered that they tolerated the treatment very poorly and the investigator made the same assessment.

When pooling the patient assessment of being acceptably well, well and very well, this proportion was 91.7% at baseline, and almost identical between the treatments at 4 weeks (95.3% on o.d. treatment vs. 96.8% on t.i.d. treatment) and 12 weeks (95.1% on o.d. treatment vs. 96.7% on t.i.d. treatment). Similarly for the investigator's assessment, the proportion of patients assessed as tolerating the treatment acceptably well, well or very well was 91.7% at baseline, and almost identical between the treatments at 4 weeks (95.2% on o.d. treatment vs. 96.6% on t.i.d. treatment) and 12 weeks (94.6% on o.d. treatment vs. 98.2% on t.i.d. treatment).

When tolerability was compared over time, no differences were seen between treatments. Over time the patient group rating o.d. as better increased; however no significant changes were observed (Figure 4). Thus the tolerability of the treatments did not differ.

Figure 4 Comparison of patient tolerability (patient assessment), o.d. vs. t.i.d. at 4, 8 and 12 weeks – ITT population



Preference

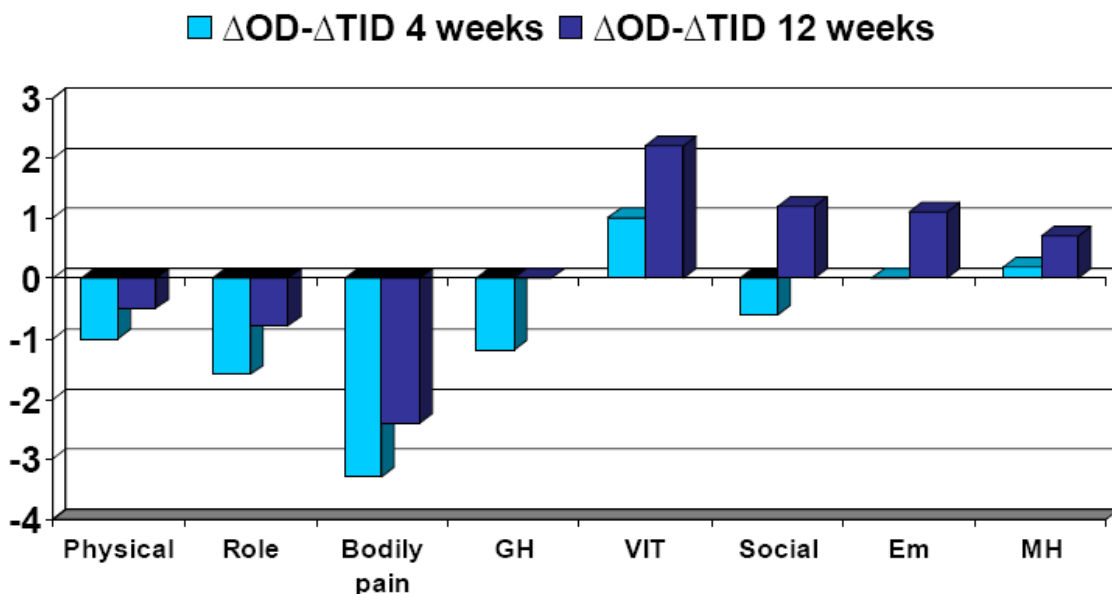
The benefit of o.d. treatment was assessed as large by 41.5% of the patients and as very large by 43.9% ($p < 0.0001$), while 4.9% of the patients found o.d. treatment to be poorer than conventional treatment and 9.8% found them comparable (ITT population). Similarly, 64.2% of the patients assessed the benefit of o.d. treatment compared to conventional treatment to be very large ($p < 0.0001$). In accordance with a majority of the patients (61.1%) answering that they preferred o.d. treatment to conventional treatment ($p < 0.0001$), a minority of the patients (8.3%) answered that they preferred conventional treatment ($p < 0.0001$). Similar results were observed in the PP population.

Quality of life (QoL)

Quality of life assessments were performed, applying three different validated instruments (SF-36, FIS and PGWB) and one instrument that have not been validated (diurnal fatigue scale).

The same pattern was seen with all the three validated instruments as exemplified by data from the SF-36 questionnaire (Figure 5). At four weeks there was a slight decrease in especially physical wellbeing. At twelve weeks this difference was less pronounced and an improvement was seen in the psychosocial domains. None of the observed differences were more than borderline significant.

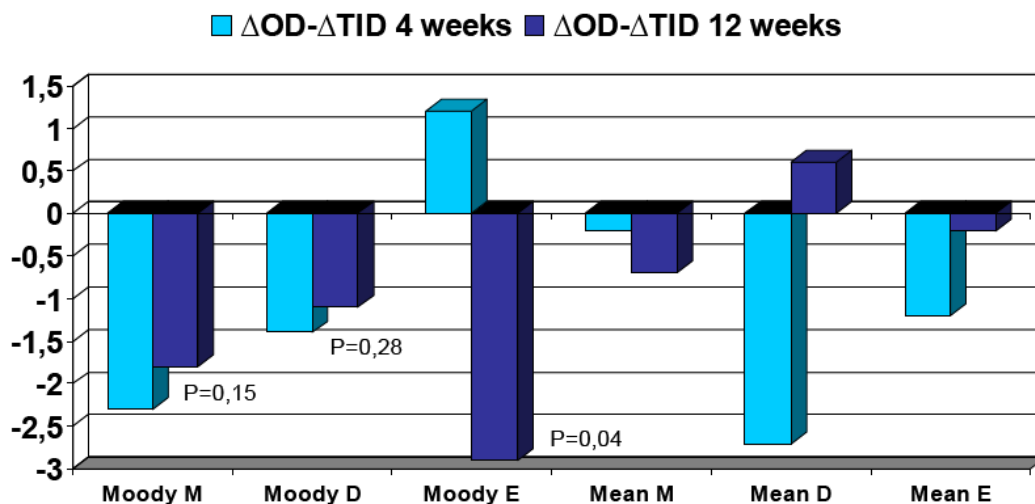
Figure 5 Difference between the treatment groups (o.d. – t.i.d.) in change from baseline to 4 and 12 weeks in QoL domains of SF-36



When applying the diurnal fatigue scale, there was a statistically significant difference in change from baseline to 12 weeks between o.d. and t.i.d. treatment with regard to VAS score for moodiness in the evening ($p=0.0366$) and mean per day ($p=0.0359$), (ITT population). As a lower value corresponds to better well-being, the patients had a more stable mood when treated with o.d. treatment, Figure 6.

No statistically significant differences were observed between o.d. and t.i.d. treatment in the PP population. The difference in total mean VAS was -0.5 mm, i.e. a small difference in favour of o.d. treatment.

Figure 6 Difference in moodiness and mean VAS between the treatment groups (o.d. – t.i.d.) in change from baseline to 4 and 12 weeks in the diurnal fatigue questionnaire



M= morning; D= day; E= evening

Note: a lower value corresponds to better well-being

Although the data on moodiness in the evening at twelve weeks were in favour of o.d., less pronounced effects were seen in the mean D and mean E scores. This might reflect the lower cortisol levels achieved by the Plenadren formulation in the afternoon.

Considering the open-label design of the study, all QoL measurements have to be interpreted with great caution. Furthermore, no correction for multiplicity was made in the statistical analysis.

Ancillary analysis

Post-hoc analyses were made for a subgroup of patients - patients with diabetes mellitus (DM). This subgroup analysis was made since this study enrolled a high percentage of patients with DM (20.6%) compared to 12%-14% in other studies described in the literature and from a safety perspective, diabetic patients with Addison's disease are more vulnerable than diabetic patients without Addison's since it is more difficult to control their glucose level and they are at increased risk of hypoglycaemia.

In this study, 17% of patients had type I diabetes and 3% had type II diabetes.

The ITT population and the safety population were identical for patients with DM.

In this subgroup, tolerability and preference was slightly lower for o.d. than in the full study population. However, numbers are small and data should be interpreted with caution.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6: Summary of Efficacy for trial DC 06/02

Title: A randomised, controlled, open, two-armed, two-period cross-over, multi-centre phase II/III study to assess the safety, tolerability and pharmacokinetics of once-daily oral modified-release hydrocortisone in comparison to conventional thrice-daily oral hydrocortisone tablets in patients with adrenal insufficiency		
Study identifier	DC 06/02	
Design	The study was conducted as an open, controlled, randomised, two-armed, two-period 12-week cross-over, multi-centre phase II/III study trial with an open 6-month extension on modified-release hydrocortisone (Plenadren).	
	Duration of main phase:	Two treatment periods of 12 weeks each (DC 06/02 Part A)
	Duration of run-in phase:	4 weeks
	Duration of extension phase:	6 months (DC 06/02 Part B)
Hypothesis	The primary efficacy endpoint of this study was the difference in multiple dose total serum (S-) cortisol AUC_{0-24h} between the novel modified-release formulation administered o.d. and conventional thrice-daily replacement therapy. The choice of the primary variable in this study was not obvious since glucocorticoids have diverse pleiotropic effects. Because of the lack of a specific biomarker for cortisol, the pharmacokinetics (PK) of cortisol is also a measure of pharmacodynamics and efficacy. The two administrations (once-daily [o.d.] and thrice-daily [t.i.d.]) result in different S-cortisol concentration-time profiles; study hypothesis therefore exploratory. The study was designed to test for a 20% difference between treatments.	
Treatment groups	Plenadren (also called o.d.)	Plenadren (oral modified-release hydrocortisone tablet administered o.d.) Duration: 12 weeks in the cross-over part, followed by a 6-month open extension on Plenadren (DC 06/02 Part B) and the option to participate in an additional open follow-up study on Plenadren (DC 08/01; ongoing, 18-month interim report available) Randomised: n=64
	t.i.d.	Conventional hydrocortisone replacement therapy administered t.i.d. Duration: 12 weeks in the cross-over part (all patients were also administered t.i.d. during the 4-week run-in period) Randomised: n=64

Endpoints and definitions	Primary endpoint	Multiple dose total S-cortisol AUC _{0-24h}	Difference in multiple dose total S-cortisol AUC _{0-24h} between Plenadren (modified-release; administered o.d.) and conventional t.i.d.
	Secondary endpoints	Secondary PK variables	Difference in: <ul style="list-style-type: none"> - maximal S-cortisol concentration (C_{max1} and C_{max2}), S-cortisol concentration at steady state (C_{ss}), first detectable S-cortisol concentration (C_{first}), C_{6h} and C_{7h} - average S-cortisol concentration during the dosing interval at steady state ($C_{ss, av}$) - time to maximal S-cortisol concentration (T_{max1} and T_{max2}), time to the first detectable S-cortisol concentration (T_{first}), time to reach a S-cortisol concentration of 200 nM (T_{200}) - terminal half life 5-24h ($t_{1/2(5-24h)}$) and 5-14h ($t_{1/2(5-14h)}$) - S-cortisol AUC_{0-4h}, AUC_{4-12h}, AUC_{6-12h}, AUC_{12-24h}, AUC_{0-10h}, AUC_{4-10h}, AUC_{6-10h}, AUC_{10-24h}, AUC_{0-inf}, AUC_{24h-inf} - AUC during a dosing interval at steady state (AUC_T) - S-cortisol AUC_T /dose, AUC_{0-24h}/dose, AUC_{0-10h} /dose, AUC_{0-4h} /dose - S-cortisol $C_{ss, av}$ /dose, C_{max1} /dose, C_{first} /dose, T_{first} /dose - % extrapol ($AUC_{(0-inf)} - AUC_{0-24h} / AUC_{0-inf}$) - Percentage fluctuation at steady state - Accumulation ratio (R_{ac})
	Other efficacy endpoints	-Tolerability -Patient preference -Quality of life (QoL) measured by SF-36, FIS, PGWB and diurnal visual analogue scale (VAS)	Difference (o.d. vs. t.i.d.) at 4 and 12 weeks: <ul style="list-style-type: none"> -Patient tolerability as by questionnaire (patient- and physician-reported) -Patient preference as by questionnaire -Well-being, i.e. QoL as by SF-36 (8 subscales and physical and mental components), FIS (3 dimensions and total score) and PGWB (6 subscales and total score) -Diurnal fatigue (VAS) (all 8 subscales)
	Safety endpoints	-Clinical laboratory parameters -Vital signs	Body weight, blood pressure and some clinical laboratory parameters (e.g. HbA1c and bone formation markers such as amino-terminal type I collagen propeptide [PINP] and osteocalcin) are related to hydrocortisone exposure.
Database lock	DC 06/02 Part A: 11-Sep-2008; DC 06/02 Part B: 06-Mar-2009		

Results and analysis				
Analysis description	Primary analysis			
Analysis population and time point description	Primary efficacy population consisted of all patients in the intent to treat (ITT) population (n=63) with complete S-cortisol profiles after multiple dosing on both Plenadren and t.i.d. treatment (n=59). The primary analysis was based on the difference between the treatments at 12 weeks.			
Descriptive statistics and estimate variability	Treatment group	Plenadren (o.d.)	t.i.d.	
	Number of subjects	59	59	
	AUC _{0-24 h} (h x nmol/l) Multiple dosage Mean	3962.0	4879.6	
	SD	1079.6	1194.4	
Effect estimate per comparison	Primary endpoint (AUC _{0-24 h})	Comparison groups	Plenadren (o.d.) vs. t.i.d.	
		Period-adjusted quotient o.d./t.i.d.	0.806	
		95% confidence interval	0.753-0.862	
		P-value	<0.0001	
Notes	Log AUC _{0-24 h} was analysed using SAS procedure PROC GLM with sequence, subject (sequence), period and treatment as class variables.			
Analysis description	Secondary PK variables: partial AUC values (average of single and multiple dosage, ITT population)			
Descriptive statistics, estimate variability, and effect estimate per comparison	Treatment group	Plenadren (o.d.)	t.i.d.	
	AUC _{0-4 h} (h x nmol/l) Mean	2053.7	1929.7	
	SD	432.0	409.9	
	AUC _{0-4 h}	Comparison groups	Plenadren (o.d.) vs. t.i.d.	
		Period-adjusted quotient o.d./t.i.d.	1.064	
		95% confidence interval	1.032-1.097	
		P-value	0.0002	
	Treatment group	Plenadren (o.d.)	t.i.d.	
	AUC _{4-12 h} (h x nmol/l) Mean	1491.8	2302.5	
	SD	638.9	669.3	
	AUC _{4-12 h}	Comparison groups	Plenadren (o.d.) vs. t.i.d.	
		Period-adjusted quotient o.d./t.i.d.	0.617	
		95% confidence interval	0.563-0.675	
		P-value	<0.0001	
Treatment group	Plenadren (o.d.)	t.i.d.		

	AUC _{12-24 h} (h x nmol/l) Mean	306.2	576.6		
	SD	305.2	681.6		
	AUC _{12-24 h}	Comparison groups		Plenadren (o.d.) vs. t.i.d.	
		Period-adjusted quotient o.d./t.i.d.		0.588	
		95% confidence interval		0.446-0.775	
		P-value		0.0003	
Notes	Only the most relevant AUC variables are presented in this table due to the large number of secondary variables in this study. Summary tables of other secondary PK variables are presented in Table xxx+1 below.				
Analysis description	Other efficacy endpoints (ITT population)				
Descriptive statistics and estimate variability	Patient preference Benefit of Plenadren (o.d.) compared to t.i.d. n (%)	Considerably poorer:		2 (3.8%)	
		Somewhat poorer		3 (5.7%)	
		Comparable		3 (5.7%)	
		Large		11 (20.8%)	
		Very large		34 (64.2%)	
Effect estimate per comparison	Patient preference at 12 weeks	Comparison groups		Plenadren (o.d.) vs. t.i.d.	
		P-value		<0.0001 (in favour of Plenadren)	
Notes	Other relevant secondary efficacy variables including tolerability and QoL are presented below due to the large number of secondary variables in this study.				
Analysis description	Safety analysis (safety population)				
Descriptive statistics, estimate variability, and effect estimate per comparison	Treatment group	Plenadren (o.d.)	t.i.d.		
	Body weight (kg) at 12 weeks Mean	78.7	79.7		
		SD	14.3	14.4	
	Body weight (kg) at 12 weeks	Comparison groups		Plenadren (o.d.) vs. t.i.d.	
		Difference Plenadren (o.d.) minus t.i.d.		-0.7	
		SD		1.7	
		P-value		0.0049	
	Treatment group	Plenadren (o.d.)	t.i.d.		
	Systolic blood pressure (mm Hg) at 12 weeks Mean	119.8	125.4		
		SD	14.5	17.7	
	Systolic blood pressure (mm Hg) at 12 weeks	Comparison groups		Plenadren (o.d.) vs. t.i.d.	
		Difference Plenadren (o.d.) minus t.i.d.		-5.5	

	SD	11.3	
	P-value	0.0001	
Treatment group	Plenadren (o.d.)	t.i.d.	
Diastolic blood pressure (mm Hg) at 12 weeks Mean	74.5	77.0	
SD	9.8	9.5	
Diastolic blood pressure (mm Hg) at 12 weeks	Comparison groups		Plenadren (o.d.) vs. t.i.d.
	Difference Plenadren (o.d.) minus t.i.d.		-2.3
	SD		8.0
	P-value		0.0343
Treatment group	Plenadren (o.d.)	t.i.d.	
HbA1c (%) at 12 weeks Mean	4.9	5.0	
SD	0.9	1.1	
HbA1c (%) at 12 weeks	Comparison groups		Plenadren (o.d.) vs. t.i.d.
	Difference Plenadren (o.d.) minus t.i.d.		-0.1
	SD		0.4
	P-value		0.0006
Treatment group	Plenadren (o.d.)	t.i.d.	
PINP (µg/l) at 12 weeks Mean	63.9	56.1	
SD	34.8	29.2	
PINP (µg/l) at 12 weeks	Comparison groups		Plenadren (o.d.) vs. t.i.d.
	Difference Plenadren (o.d.) minus t.i.d.		6.1
	SD		15.5
	P-value		0.0036
Treatment group	Plenadren (o.d.)	t.i.d.	
Osteocalcin (µg/l) at 12 weeks Mean	13.4	12.4	
SD	6.5	5.4	
Osteocalcin (µg/l) at 12 weeks	Comparison groups		Plenadren (o.d.) vs. t.i.d.
	Difference Plenadren (o.d.) minus t.i.d.		0.7
	SD		4.5
	P-value		0.2337

Clinical studies in special populations

No studies have been performed in special populations, which is acceptable.

Supportive studies

Study DC 06/02, Part B

After the second cross-over treatment period in Part A, patients continued in a 6-month open extension part on the novel o.d. modified-release hydrocortisone treatment. At the first 3-month visit, a full clinical examination took place with full laboratory assessments, study drug dispensation, AE assessment and collection of patient questionnaires including diurnal fatigue score. Identical assessments were performed after the second 3-month open controlled treatment period. During the 6-month period, all periods with intercurrent illness and periods of increased cortisol need and the outcome of these events were recorded.

No modifications to the treatment were made, thus the patients were maintained on the o.d. dose they had received during Part A of the study. No reference drug was used in Part B.

The secondary efficacy assessments in Part B consisted of the following:

- tolerability and safety;
- tolerability and safety at intercurrent illness dosage ;
- well-being, as assessed by SF-36, FIS and PGWB;
- diurnal fatigue score (VAS scale);
- compliance.

It should be taken into consideration that both the QoL assessment and safety assessment could be hampered by the open-label design and the fact that five patients declined participation in part B. Thus 59 patients were included in Part B. Two patients discontinued from the study.

Table 7 Disposition of patients

Patients included in Part B of the study	59 (100.0%)
Intent-to-treat Population	58 (98.3%)
Per Protocol Population	53 (89.8%)
Safety Population	59 (100.0%)
Patients Discontinued from Study	2 (3.4%)

Measurements of the treatment compliance

Compliance was calculated as days during the study period multiplied by the daily hydrocortisone use yielding the expected cortisol consumption. Mean treatment compliance was very similar to what was seen in Part A, however the range in the extension study was much larger, indicating the use of additional hydrocortisone as well as more skipped doses than observed in the first part of the study.

Table 8 Treatment compliance

	Safety population (n=59)	
	Mean (SD) Median (Min; Max)	p-value within group
Compliance 3 months follow-up o.d.	102.9 (16.5) 100.0 (64.3; 155.0) n=58	
Compliance 6 months follow-up o.d.	102.3 (12.8) 100.3 (61.6; 142.4) n=58	
Difference in compliance 3 months follow-up o.d. vs. 6 months follow-up o.d.	0.527 (19.712) 0.681 (-46.192; 74.065) n=58	0.9269

For continuous variables Mean (SD) / Median (Min; Max) / n= are presented.

For comparison over time within groups Wilcoxon Signed Rank test was used.

Patient Tolerability over Time (Part A and Part B)

The analysis of change from baseline in Part A to end of treatment at 6 months in Part B showed that a majority of patients, 56.6%, reported no change in tolerability while 28.3% reported an improvement and 15.1% reported a worsening in tolerability (p=0.2100). The investigator assessment was similar to the patient assessment.

Quality of Life (QoL) assessment over Time (Part A and Part B)

The QoL assessments were generally stable over time and the only statistically significant change observed was an increase in bodily pain (-6.14; p=0.0032) in the SF-36 questionnaire.

Diurnal Fatigue over Time (Part A and Part B)

The VAS QoL variables were overall stable and showed little change over time in Part B. From baseline in Part A to end of treatment in Part B statistically non-significant improvements in mean VAS scores of diurnal fatigue were observed for morning (-2.58; p=0.2966), day (-1.76; p=0.4832), evening (-2.17; p=0.2047) and day average (-2.46; p=0.2933). Statistically significant improvements were observed for the variable energy in the morning, day and day average.

Study DC 08/01

This ongoing study is conducted as an open, multi-centre, phase III, long-term follow-up study in patients with adrenal insufficiency. A total of 18 months follow-up data have been provided from this study so far.

All patients who completed study DC 06/02, fulfilled all inclusion criteria and no exclusion criteria and gave their consent were consecutively enrolled in the study on the day of completion of the open extension phase of the DC 06/02 study. Fifty-five patients accepted to continue in study DC 08/01.

In addition, approximately 30 patients who were screened but not randomised in study DC 06/02 were asked to participate in this study. These patients were enrolled in this study if giving their informed consent and fulfilling all inclusion criteria and no exclusion criteria. A higher proportion of patients were on 20-25 mg per day at inclusion compared to patients included in study 06/02.

In total 71 patients have been included in the study, of whom 68 have completed the first six months of study treatment. Sixty-seven patients have completed 18 months of follow-up.

In this study, dose adjustments could be made according to the treating physician's judgment according to clinical symptoms and signs associated with glucocorticoid excess and glucocorticoid deficiency.

Efficacy Results up to and Including the 6-Month Interim Analysis

Tolerability and measures of self-perceived QoL were overall stable and showed statistically significant

improvements in some of the QoL parameters in the full safety population. The proportion of patients rating the tolerability as very well, well or acceptable was 98.5% at baseline. The analysis of change in patient tolerability from 0 to 6 months showed that 77% of patients reported no change in tolerability and a higher percentage of patients reported an improvement, 19%, compared to a worsening in tolerability, 5%, (p-value patient assessment: 0.04; p-value investigator assessment: 0.008). The newly recruited patients reported no statistically significant change in tolerability while the investigator assessment of patient tolerability from 0 to 6 months showed an improvement in 46% of the newly recruited patients vs. a worsening in 0% (p=0.03).

Neither in the full safety population, nor in the newly recruited patients, was any statistically significant change observed in the FIS domains. There was a statistically significant improvement in the PGWB domains anxiety (p=0.03), depressed mood (p=0.005), positive well-being (p=0.02), vitality (p=0.007) and total score (p=0.006) from 0 to 6 months. The analysis of newly enrolled patients showed a statistically significant improvement in anxiety (p=0.008) and a statistically significant worsening in self-control (p=0.03).

Efficacy Results up to and including the 18-Month Interim Analysis

The proportion of patients rating the tolerability as very well, well or acceptable was 98.5% at baseline. The analysis of change in patient tolerability from 0 to 18 months showed that 67% of patients reported no change in tolerability, 20% reported an improvement and 12 % reported a worsening in tolerability. The investigator assessment was similar to the patient assessment, (p-value patient assessment: 0.38; p-value investigator assessment: 0.18).

A worsening was observed in the FIS variables psychosocial functioning (2.1; p=0.04) and the total score (4.3; p=0.03) in the full safety population from start of DC 08/01 to 18 months. No statistically significant changes were observed in the FIS variables from baseline in DC 06/02 Part A. The PGWB scores were stable over time without any statistically significant changes from start of DC 08/01 to 18 months or from baseline in DC 06/02 Part A to 18 months in DC 08/01.

Dose Adjustments

In this study change of daily dose of study medication was allowed. Nineteen patients changed the daily dose during the study of whom 9 patients changed the maintenance dose more than once during the study. Overall, 9 patients had a decrease in the maintenance dose, 6 had an increase and 4 changed the maintenance dose and then reverted during the 18-month period to the dose at start of DC 08/01.

2.4.7 Discussion on clinical efficacy

PK data has to be interpreted with caution due to deficiencies with reference to the methods used to measure cortisol (see pharmacokinetic assessment). It appears that the exposure of Plenadren is about 20 % lower than the same daily dose as conventional therapy. The achieved profile exhibits a high peak in the morning and a slow decline during the afternoon with once daily treatment, thereby partly mimicking the physiological profile. Cortisol levels are maintained during the day without the increased cortisol levels in the afternoon seen with t.i.d. treatment. However, as also can be seen in Figure 7, the cortisol levels are higher than the levels observed in healthy volunteers in the morning. Furthermore, cortisol levels with Plenadren are lower than observed in healthy volunteers during the afternoon and evening.

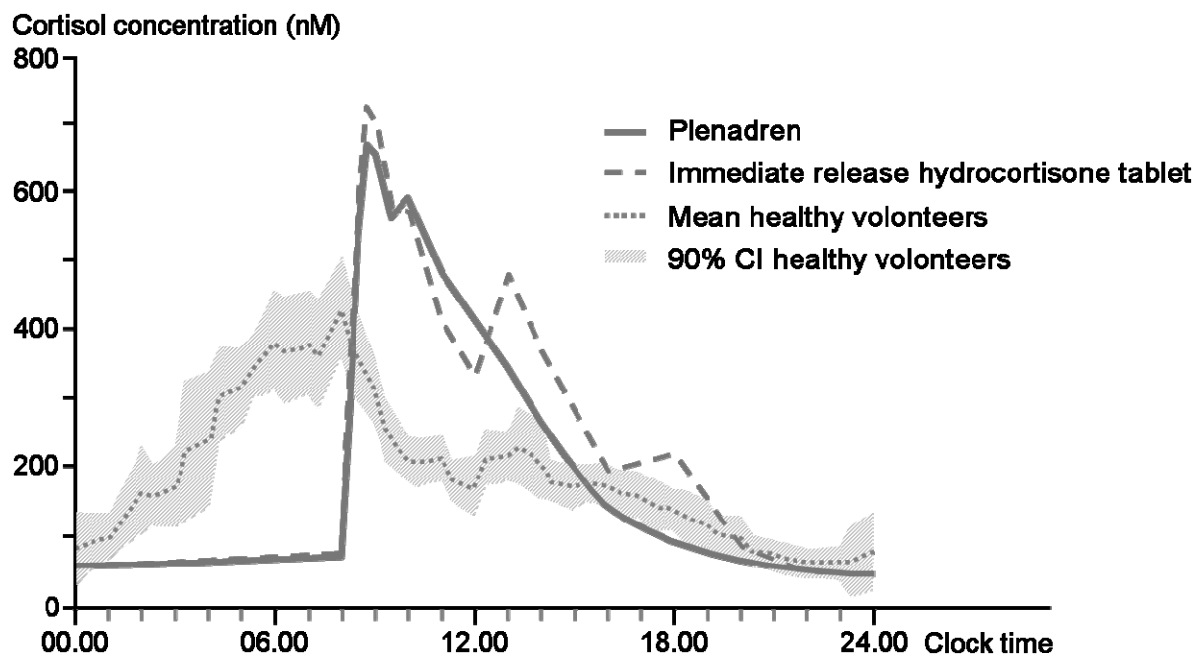


Figure 7. Observed mean serum cortisol concentration versus clock time in primary adrenal insufficiency patients (n=62) after oral administration of Plenadren once daily, hydrocortisone tablets thrice daily and healthy volunteers (HV; n=13). CI=confidence interval.

Furthermore, the gradual build up to the morning cortisol peak (normally starting at the 3rd hour of sleep) and the 2 daytime spikes – associated with eating, especially high protein content food – seen in normal endogenous cortisol secretion are missing from the curve produced by Plenadren. Thus, no claim for a physiological PK profile can be made.

The enrolled patients in the clinical studies DC 06/02 and DC 08/01 were to maintain their ordinary hydrocortisone dose at inclusion and in study DC 06/02 no changes in dose were allowed throughout the study. Doses ranging from 15 to 40 mg were allowed (20-40 mg in DC 06/02 and 15-40 mg in DC 08/01), and the only change made to the treatment was the fact that all patients were to be using a t.i.d. regimen.

The dose was not allowed to be changed from the dose at baseline in study DC06/02. However, dose changes are allowed in the ongoing open-label study 08/01. Scarce titration data have been provided from the 18 month follow-up of this study. The majority of patients maintained their initial dose when changing from conventional therapy to Plenadren. Of patients who had their dose changed, 9/71 had their dose decreased whereas 6/71 had their dose increased. It therefore appears that patients may be switched from t.i.d. to o.d. on a milligram basis, although some patients may experience a worsening of symptoms. This is indicated by the fact that five patients in study 06/02 actively changed from o.d. to conventional treatment and two patients in study 08/01 withdrew due to impaired wellbeing.

The secondary clinical efficacy parameters relate to tolerability, preference and QoL. When patients are switched from t.i.d. to once daily it appears that a number of patients experience a decrease in QoL during the first four weeks. The reason for this is unclear. It may have to do with the patient's expectations; however, the most prominent worsening was seen in the physical parameters which may indicate some cortisol withdrawal symptoms. On the other hand, patient's preference lay with Plenadren, which may be due to a simpler dosing. The QoL results were very consistent over the study programme but have to be interpreted with caution due to the small number of patients and the open

design of the studies. The uncontrolled QoL data from the 18-month follow-up showed only a significant worsening of the parameter psychosocial functioning of one of the two instruments applied, whereas all other parameters remained unchanged compared to baseline.

An inherent feature of a modified-release tablet in general is that it offers less flexibility when it comes to individual dose adjustment over the day; not just in terms of the dose given but also in terms of the timing of taking hydrocortisone. As a result, the obtained concentration time profile may not be suitable for all patients based on the use of Plenadren alone; however, drop-out rates were low in the studies.

Due to the fixed dosing in studies DC 06/02 Part A and B, the only data available on dose titration with Plenadren is scarce information from study DC 08/01. Considering the 20 % lower cortisol exposure with Plenadren compared to hydrocortisone, it may be expected that some of the worsening may be overcome by increasing the dose. The data from the open-label long-term follow-up study show that the majority of patients maintain an unchanged dose and in the patients who did change their dose, a slightly higher number had their dose decreased rather than increased.

Initially there were major concerns due to the lack of a clear statement of the primary objective of Study DC 06/02 Part A in terms of superiority, equivalence or non-inferiority of the new formulation compared to the conventional therapy in terms of the primary endpoint. The Applicant has provided further details of the statistical methods used to resolve this issue. Initially there was still some concern expressed over the discrepancy between the strategy adopted by the Applicant and the advice provided by the CHMP. However, considering the legal basis of the application (hybrid) there is no requirement for (bio)equivalence to be shown and the CHMP was of the opinion that the PK profile has been sufficiently characterised and is well reflected in the SmPC.

The adequacy of the single primary endpoint has been discussed above. The results of the primary analysis clearly indicate that the once daily formulation has a statistically, significantly lower bioavailability than the conventional therapy. Considering that an important drawback identified with the conventional therapy is over-substitution, the lower exposure related to the bioavailability may be of benefit as long as there are no indications of significant under-substitution in the individual patient.

2.4.8 Conclusions on clinical efficacy

The proposed beneficial effect of Plenadren compared to conventional treatment is the fact that a more physiological profile of the replacement therapy may transform into a more favourable metabolic profile which eventually could result in a decrease in morbidity and mortality in the target population while still providing a sufficient cortisol replacement. In this context a lower bioavailability and exposure may be of benefit since one important drawback with conventional therapy is long-term effects suggestive of over-substitution. However, the clinical data is insufficient to make any claims on improvements with regards to metabolic side effects with Plenadren (see further discussion on clinical safety).

A once daily dosing regime could potentially be of benefit in the context of convenience and patient compliance provided that there are no indications of clinically significant over- or under-substitution. The simpler dosing regimen is reflected in a higher patient's preference, however, no clinically significant improvement in QoL could be observed.

The titration of the cortisone dose in clinical practice is always performed on an individual basis. To permit appropriate clinical use, a new formulation needs to be sufficiently well characterised, but there is no absolute need for the new formulation to be similar to other formulations. In view of the different release of the different pharmaceutical forms the bioequivalence cannot be demonstrated, but the

product should be sufficiently characterised with regards to pharmacokinetics. The CHMP is of the opinion that the PK profile has been sufficiently characterised and is well reflected in the SmPC.

Due to the differences in the PK profile, when compared to the physiological cortisol profile, no claim of a full resemblance to the physiologic release pattern can be made for Plenadren.

The efficacy data presented concerning tolerability and wellbeing should be interpreted with caution due to the open-label design of the studies. The data indicate that a majority of patients may be switched to Plenadren on a milligram basis; however some patients apparently experience a worsening in wellbeing. This may be due to the lower cortisol exposure, which appears to be most prominent in the afternoon. Although data does not allow for any detailed recommendations on titration of the dose, this issue has been handled by amending the SmPC with adequate information, including the possibility to combine Plenadren with IR hydrocortisone.

2.4.9 Clinical safety

Patient exposure

Phase I study

The safety population of the first part of the phase I study DC 06/01 (5 mg vs. 20 mg, single dose administrations) includes 16 healthy volunteers and the second part of the phase I study DC 06/01 (20 mg in the fasted state vs. 20 mg with food, single dose administrations) includes 14 subjects.

Forty-seven non-serious treatment-emergent AEs were reported. No serious AEs (SAEs) were reported in that study. As the recorded AEs in the healthy volunteer study were transient, of mild or moderate intensity and predominantly procedure-related (i.e., sampling-related such as cannula related haematomas and transient low haemoglobin values), this section hereafter focuses on the studies including patients with AI.

Phase II/III studies

Eighty patients with primary AI received at least one dose of o.d. treatment in DC 06/02 and/or DC 08/01. The most common daily dose at start of study drug was 30 mg. Up to the 6-month interim analysis in DC 08/01, the mean number of days on o.d. treatment was 356 days. The total exposure up to and including the 6-month interim analysis in DC 08/01 corresponds to 78 patient years. At that time point, 68 patients had received o.d. treatment for at least 6 months and 54 patients had received o.d. treatment for at least one year, Table 9.

The Applicant has provided data from the 18 month follow-up of study DC 08/01 and the total patient exposure now amounts to approximately 145 patient years.

Fifty-five of the 64 patients included in study DC 06/02 both completed that study and were included in study DC 08/01 of whom 54 patients received study drug for at least 12 months. With the additional data from the 18 month follow-up the number of patients who have received the drug for more than one year, amounts to 68 patients.

Table 9 Extent of exposure, by dose - safety population

Daily dose (mg)	No. of treated patients (i.e., No. of patients receiving at least one dose o.d.) n (%)	Mean No. of days on o.d. treatment Mean (SD)/ Median (Min; Max)/ n	Patient years (o.d.)	Patients receiving o.d. treatment for at least 6 months n (%)	Patients receiving o.d. treatment for at least 1 year n (%)
20 mg	13 (16.3%)	341.0 (131.7) 443 (170;466) n=13	12.14	11 (16.2%)	7 (13.0%)
25 mg	12 (15.0%)	293.3 (165.9) 309 (2;476) n=12	9.63	9 (13.2%)	6 (11.1%)
30 mg	39 (48.8%)	386.0 (118.6) 437 (66;492) n=39	41.22	35 (51.5%)	30 (55.6%)
35 mg	2 (2.5%)	193.0 (14.1) 193 (183;203) n=2	1.06	2 (2.9%)	0 (0.0%)
40 mg	14 (17.5%)	362.4 (161.0) 426 (35;473) n=14	13.89	11 (16.2%)	11 (20.4%)
Total	80 (100.0%)	355.8 (138.8) 435.5 (2;492) n=80	77.94	68 (100.0%)	54 (100.0%)

Please note that the daily dose is the starting dose and that changes in dose are not captured here, (e.g. one patient received a dose of 60 mg on one occasion in connection with PK sampling).

In the cross-over study (DC 06/02 Part A), the mean total hydrocortisone exposure during 12 weeks treatment was similar during o.d. (2627 mg) and t.i.d. treatment (2584 mg). The total value takes into account both dose adjustments and extra doses (both illness and non-illness related). Furthermore, the mean ordinary hydrocortisone usage (i.e., the amount of hydrocortisone usage based on the prescribed daily replacement dose) was similar during o.d. (2572 mg) and t.i.d. treatment (2552 mg). The mean increased hydrocortisone usage dose (extra doses at need) was 29.6 mg during o.d. treatment and 31.1 mg during t.i.d. treatment. Also the mean increased hydrocortisone dose due to intercurrent illness was similar during o.d. (111 mg) and t.i.d. treatment (112 mg).

The extent of exposure during each 3-month period in DC 06/02 Part B and each 3-month period in DC 08/01 was similar to that observed in DC 06/02 Part A while the mean total hydrocortisone dose was lower, especially during the first 3-month period, in newly recruited patients in DC 08/01 (2233 mg). The mean increased hydrocortisone usage dose (extra doses at need) was higher in newly recruited patients in DC 08/01 but it should be noted that only a few patients took extra doses (n=5 during the first and n=3 during the second 3-month period). Notably, more patients in the newly recruited group of patients were on a basal dose of 20 mg than among the patients recruited from study DC 06/02.

Adverse events

In the cross-over study (DC 06/02 Part A), 46 of the 64 AI patients (72%) reported a total of 99 non-serious AEs on o.d. treatment compared to 42 patients (66%) who reported a total of 74 non-serious AEs on t.i.d. treatment. The most commonly reported preferred terms were nasopharyngitis (7 patients on o.d. treatment and 15 on t.i.d.), fatigue (8 patients on o.d. treatment and 3 on t.i.d.) and influenza (8 patients on o.d. treatment and 2 on t.i.d.).

A total of 296 AEs were reported from baseline in DC 06/02 Part A up to and including the 6-month interim analysis in DC 08/01. Four of these AEs were reported after database closure of DC 06/02 Part B (all of them were assessed as not related to the study treatment and were of mild intensity). Thus, up to database closure, 292 AEs were reported by 74 patients (93%) on o.d. treatment. The most commonly reported preferred terms reported during o.d. treatment from baseline in DC 06/02 Part A and up to and including the 6-month interim analysis in DC 08/01 were nasopharyngitis with 41 events reported by 27 patients (34%), fatigue with 20 events reported by 17 patients (21%) and influenza with 17 events reported by 16 patients (20%).

Fatigue was the most commonly reported AE apart from infectious disorders, and fatigue was also more common in the o.d. treated group.

The frequency of AEs over time was highest during the first 3-month period when 72% of patients on o.d. and 66% of patients on t.i.d. reported any AE. Thereafter, the percentage of patients reporting AEs was lower and varied between 44% and 51% per 3-month period, which was below the frequency on t.i.d. in DC 06/02 Part A. The pattern of higher frequency of AEs during the first 3-month period after treatment switch was observed also in the newly recruited patients in DC 08/01 with 11 of 16 patients (69%) reporting any AE during the first 3-month period and 6 of 14 (43%) reporting any AE during the second 3-month period.

Within the first 3-month period of treatment, there was a trend of AEs being more commonly reported during the first 4 weeks (38% on o.d. and 30% on t.i.d.) of the treatment period and during weeks 4-8 (36% on o.d. and 20% on t.i.d.) than during weeks 8-12 (25% on o.d. and 27% on t.i.d.), Table 10.

These data are in line with the QoL assessments. The reporting pattern may be affected by the open-label design of the study, however, it cannot be excluded that patients actually are negatively affected by the transition from t.i.d. to o.d.

Table 10 No. of patients with non-serious AEs in DC 06/02 Part A, by treatment and onset - safety population

	o.d. (n=64)						t.i.d. (n=64)					
	0-4w		4-8w		8-12w		0-4w		4-8w		8-12w	
	No. of AEs	Patients with AEs n (%)	No. of AEs	Patients with AEs n (%)	No. of AEs	Patients with AEs n (%)	No. of AEs	Patients with AEs n (%)	No. of AEs	Patients with AEs n (%)	No. of AEs	Patients with AEs n (%)
Any AE	32	24 (37.5%)	30	23 (35.9%)	22	16 (25.0%)	31	19 (29.7%)	13	13 (20.3%)	21	17 (26.6%)

In the cross-over study (DC 06/02 Part A), 26 treatment-emergent non-serious AEs reported by 21 patients (33%) during o.d. treatment and 12 AEs reported by 11 patients (17%) during t.i.d. treatment were assessed as at least possibly related to the study treatment. The preferred terms most commonly assessed as at least possibly related to study drug were fatigue (reported by 7 patients on o.d. and 2 patients on t.i.d.), nausea (reported by 3 patients on o.d. and 1 patient on t.i.d.) and vertigo (1 patient on o.d. and 2 patients on t.i.d.).

A total of 71 treatment-emergent non-serious AEs assessed as at least possibly related to the o.d. treatment were reported by 37 patients (46%) from baseline in DC 06/02 and up to and including the 6-month interim analysis in DC 08/01, i.e., over a period covering 15 months on o.d. treatment. The preferred terms most commonly assessed as at least possibly related to study drug were fatigue with 14 AEs reported by 12 patients (15%), vertigo with 9 AEs reported by 8 patients (10%) and diarrhoea with 4 AEs reported by 3 patients (4%).

As for AEs of any relationship to study drug, the frequency of AEs assessed as at least possibly related to o.d. treatment was highest during the first 3-month period (33% in DC 06/02 Part A and 44% in

newly recruited patients in DC 08/01). Thereafter, the percentage of patients reporting AEs varied between 8% and 21% per 3-month period.

Serious adverse events and deaths

A total of 17 SAEs were reported by 17 patients (21%) during o.d. treatment from baseline up to and including the 6-month interim analysis in DC 08/01. The most commonly reported preferred term was gastroenteritis with 6 SAEs reported by 6 patients (8%). No other preferred term was reported affected by more than one SAE.

During the cross-over period (DC 06/02 Part A), 6 of the 64 patients (9%) reported 6 SAEs on o.d. treatment compared to 2 patients (3%) who reported 2 SAEs on t.i.d. treatment (Table 11). The SAEs occurring during o.d. treatment included four cases of gastroenteritis, one case of bacterial bronchitis due to influenza and one case of pneumonia. The SAEs occurring during t.i.d. treatment included two cases of gastroenteritis. No plausible explanation could be found for the uneven distribution of SAEs between the treatments in DC 06/02 Part A. Thus, all SAEs in DC 06/02 Part A were caused by infectious disorders and the patients were hospitalised to prevent/treat a state of acute AI.

Table 11 Treatment-emergent SAEs – safety population

	DC 06/02 Part A 0-3 months t.i.d. (n=64)		DC 06/02 Part A 0-3 months o.d. (n=64)		DC 06/02 Part B 0-3 months o.d. (n=59)		DC 06/02 Part B 3-6 months o.d. (n=57)		DC 08/01 0-3 months o.d. Patients from DC 06/02 (n=55)		DC 08/01 3-6 months o.d. Patients from DC 06/02 (n=54)		DC 08/01 0-3 months o.d. Newly recruited patients (n=16)		DC 08/01 3-6 months o.d. Newly recruited patients (n=14)		Total o.d. (n=80)	
	No. of SAEs	Pat with SAEs n (%)	No. of SAEs	Pat with SAEs n (%)	No. of SAEs	Pat with SAEs n (%)	No. of SAEs	Pat with SAEs n (%)	No. of SAEs	Pat with SAEs n (%)	No. of SAEs	Pat with SAEs n (%)	No. of SAEs	Pat with SAEs n (%)	No. of SAEs	Pat with SAEs n (%)	No. of SAEs	Pat with SAEs n (%)
Any SAE	2	2 (3.1%)	6	6 (9.4%)	2	2 (3.4%)	4	4 (7.0%)	2	2 (3.6%)	2	2 (3.7%)	0	0 (0.0%)	1	1 (7.1%)	17	17 (21.3%)

A lower frequency of SAEs than that observed during o.d. treatment in DC 06/02 Part A was observed during o.d. treatment in the subsequent study periods, also in the newly recruited patients in DC 08/01 (Table 11).

From baseline up to and including the 6-month interim analysis in DC 08/01, i.e., over 18 months, three SAEs were assessed as possibly related to the study treatment (one acute AI due to gastroenteritis and two cases of gastroenteritis). No SAE occurring during t.i.d. treatment was assessed as possibly related to the treatment.

From baseline up to and including the 6-month interim analysis in DC 08/01, 9 of the 17 SAEs occurring during o.d. treatment were of severe intensity and 8 were of moderate intensity. One of the two SAEs occurring during t.i.d. treatment was of severe intensity and one was of mild intensity.

Deaths

No deaths were recorded in study DC 06/01 or DC 06/02. Two deaths, one due to subarachnoid haemorrhage, occurring 22 days after stop of study treatment and one due to fall from height, both assessed as not related to the study treatment, were reported during the 18 months of study DC 08/01.

Intercurrent illness and non-illness related increased hydrocortisone usage

In patients with AI, extra doses of hydrocortisone are needed in the event of an intercurrent illness or during extraordinary physical or mental stress. One aim of study DC 06/02 was to assess the safety and tolerability of using the novel modified-release formulation as “rescue therapy” during minor intercurrent illnesses in patients with primary AI.

Intercurrent illness data were based on a questionnaire on intercurrent illness and should, according to the Applicant, be separated from conventional AEs. However, some intercurrent illnesses develop into conventional AEs and in case of discrepancies between the patient diary and the AE report, the investigator was prompted to reinvestigate any preceding AEs. The Applicant has reported all intercurrent illness episodes with a similar starting date as a reported AE. None of the reported SAEs appears to have been preceded by an AE. All but three reported episodes of intercurrent illness, which all occurred during o.d. treatment, were also reported as AEs. In all three episodes the patient had reported a common cold.

In total, the mean number of episodes of increased hydrocortisone usage due to intercurrent illness was 3.7 per patient, the mean number of days per episode of increased hydrocortisone usage due to intercurrent illness was 2.8 and the mean dose of hydrocortisone per episode of increased usage due to intercurrent illness was 19.6 mg, Table 12. There were no apparent differences between the treatment groups during Part A of study DC 06/02.

Table 12 Intercurrent illness and increased hydrocortisone usage due to intercurrent illness, by time period – safety population

	0-3 months DC 06/02 Part A (patients randomised to t.i.d. in the first 3-month period) t.i.d. (n=32)	0-3 months DC 06/02 Part A (patients randomised to o.d. in the first 3-month period) o.d. (n=32)	3-6 months DC 06/02 Part A (patients randomised to t.i.d. in the first 3-month period) o.d. (n=32)	3-6 months DC 06/02 Part A (patients randomised to o.d. in the first 3-month period) t.i.d. (n=32)	0-3 months DC 06/02 Part B (o.d.) (n=59)	3-6 months DC 06/02 Part B (o.d.) (n=57)	0-3 months DC 08/01 (patients recruited from DC 06/02) (o.d.) (n=55)	3-6 months DC 08/01 (patients recruited from DC 06/02) (o.d.) (n=54)	0-3 months DC 08/01 (newly recruited patients) (o.d.) (n=16)	3-6 months DC 08/01 (newly recruited patients) (o.d.) (n=14)	Total o.d. (n=80)
Total No. of episodes of increased usage	18	33	21	15	21	26	26	12	17	19	208
Total No. of pat with increased usage	7	16	9	11	13	14	17	11	8	5	56
Total No. of days of increased usage per period	60	76	61	27	52	74	57	52	39	62	560
Mean No. of episodes per pat	2.57 (2.44) 2.0 (1.0; 8.0) n=7	2.06 (2.05) 1.0 (1.0; 9.0) n=16	2.33 (1.73) 2.0 (1.0; 6.0) n=9	1.36 (0.50) 1.0 (1.0; 2.0) n=11	1.62 (0.65) 2.0 (1.0; 3.0) n=13	1.86 (1.29) 1.0 (1.0; 5.0) n=14	1.53 (0.87) 1.0 (1.0; 3.0) n=17	1.09 (0.30) 1.0 (1.0; 2.0) n=11	2.13 (1.13) 2.0 (1.0; 4.0) n=8	3.80 (4.09) 1.0 (1.0; 10.0) n=5	3.71 (2.99) 3.0 (1.0; 14.0) n=56
Mean No. of days/episode	4.95 (6.81) 2.0 (1.0; 20.0) n=7	2.30 (1.69) 2.0 (1.0; 8.0) n=16	2.85 (1.48) 2.7 (1.0; 5.0) n=9	1.95 (0.99) 1.5 (1.0; 4.0) n=11	2.76 (2.07) 2.0 (1.0; 7.0) n=13	2.94 (2.01) 3.1 (1.0; 7.0) n=14	2.37 (1.41) 2.0 (1.0; 6.0) n=17	4.64 (6.09) 3.0 (1.0; 22.0) n=11	2.28 (0.94) 2.0 (1.5; 4.5) n=8	2.91 (1.54) 2.8 (1.0; 5.0) n=5	2.81 (2.78) 2.2 (1.0; 20.0) n=56
Mean dose/episode (mg)	22.50 (14.65) 20.0 (5.0; 45.0) n=7	24.25 (10.84) 20.0 (5.0; 40.0) n=16	20.09 (8.23) 20.0 (5.0; 30.0) n=9	16.14 (11.14) 10.0 (5.0; 40.0) n=11	19.62 (10.50) 20.0 (5.0; 40.0) n=13	16.38 (9.37) 14.0 (5.0; 40.0) n=14	20.83 (8.24) 20.0 (5.0; 30.0) n=17	14.85 (12.64) 11.7 (5.0; 40.0) n=11	26.11 (14.51) 21.7 (15.0; 60.0) n=8	19.74 (12.59) 20.0 (7.5; 40.0) n=5	19.63 (9.70) 20.0 (5.0; 60.0) n=56

For continuous variables Mean (SD) / Median (Min; Max) / n are presented.

Increased Hydrocortisone Usage

Non-illness related increased hydrocortisone usage was also assessed during the studies (referred to as "Increased Hydrocortisone Usage"). In the cross-over study (DC 06/02 Part A), the total number of episodes of increased hydrocortisone usage was higher during o.d. treatment (40 episodes in 21 patients when combining the first and second o.d. period) than during t.i.d. treatment (17 episodes in 9 patients). Also the total number of days of increased hydrocortisone usage differed (95 days vs. 20 days). The higher number of days of increased hydrocortisone usage during o.d. treatment was partly caused by one patient, who had one 25-day period of increased hydrocortisone usage during the o.d. period due to physical exercise and high altitude sickness when walking in the Himalayan mountains. The number of days with increased hydrocortisone usage has to be viewed in the perspective of the total number of treatment days per period, i.e., 5376 days (64 patients x 12 weeks x 7 days). It is difficult to with certainty make any conclusions regarding causality due to the bias from the open study design.

During the cross-over study, the mean number of episodes of increased hydrocortisone usage per patient was similar between the treatments (approximately 2) and the mean number of days of

increased hydrocortisone usage per episode ranged from 1.1 to 3.2 days. The mean dose of hydrocortisone per episode was also similar between the treatments and ranged from 9 mg to 19 mg.

In the subsequent 3-month periods, the mean number of episodes per patient ranged from 2.3 to 3.6 (5.4 in newly recruited patients in DC 08/01) and the number of days/episode ranged from 1.1 to 6.1 per 3-month period. The mean dose of hydrocortisone per episode was similar over the 3-month periods and ranged from 9 mg to 16 mg, Table 13.

Approximately half of the increased hydrocortisone usage was due to physical stress and half due to mental stress.

Table 13 Increased hydrocortisone usage, by time period – safety population

	0-3 months DC 06/02 Part A (patients randomised to t.i.d. in the first 3-month period) t.i.d. n=32	0-3 months DC 06/02 Part A (patients randomised to o.d. in the first 3-month period) o.d. n=32	3-6 months DC 06/02 Part A (patients randomised to t.i.d. in the first 3-month period) o.d. n=32	3-6 months DC 06/02 Part A (patients randomised to o.d. in the first 3-month period) t.i.d. n=32	0-3 months DC 06/02 Part B (o.d.) n=59	3-6 months DC 06/02 Part B (o.d.) n=57	0-3 months DC 08/01 (patients recruited from DC 06/02) (o.d.) n=55	3-6 months DC 08/01 (patients recruited from DC 06/02) (o.d.) n=54	0-3 months DC 08/01 (newly recruited patients) (o.d.) n=16	3-6 months DC 08/01 (newly recruited patients) (o.d.) n=14
Total No. of episodes of increased usage	11	18	22	6	23	32	32	20	27	13
Total No. of pat with increased usage	4	9	12	5	10	11	9	8	5	3
Total No. of days of increased usage per period	13	28	67	7	79	37	34	31	56	54
Mean No. of episodes per pat	2.75 (2.06) 2.5 (1.0; 5.0) n=4	2.00 (1.22) 2.0 (1.0; 5.0) n=9	1.83 (1.03) 1.5 (1.0; 4.0) n=12	1.20 (0.45) 1.0 (1.0; 2.0) n=5	2.30 (2.79) 1.0 (1.0; 10.0) n=10	2.91 (3.21) 2.0 (1.0; 11.0) n=11	3.56 (4.39) 1.0 (1.0;14.0) n=9	2.50 (1.93) 2.0 (1.0;6.0) n=8	5.40 (5.68) 2.0 (1.0;13.0) n=5	4.33 (3.51) 4.0 (1.0;8.0) n=3
Mean No. of days/ episode	1.13 (0.25) 1.0 (1.0; 1.5) n=4	1.56 (1.21) 1.0 (1.0; 4.5) n=9	3.19 (4.35) 1.0 (0.7; 15.0) n=12	1.20 (0.45) 1.0 (1.0; 2.0) n=5	6.06 (14.75) 1.0 (1.0; 48.0) n=10	1.33 (0.90) 1.0 (1.0; 4.0) n=11	1.13 (0.33) 1.0 (1.0;2.0) n=9	2.08 (1.60) 1.1 (1.0;5.0) n=8	1.71 (0.76) 1.8 (1.0;2.8) n=5	3.29 (2.45) 3.0 (1.0;59) n=3
Mean dose/ episode (mg)	18.63 (16.10) 14.8 (5.0; 40.0) n=4	17.22 (11.21) 20.0 (5.0; 40.0) n=9	9.10 (7.07) 7.5 (4.2; 30.0) n=12	16.00 (10.84) 10.0 (5.0; 30.0) n=5	12.50 (10.87) 10.0 (5.0; 40.0) n=10	9.19 (3.35) 10.0 (5.0; 15.0) n=11	15.53 (14.25) 6.7 (5.0;40.0) n=9	13.00 (12.33) 8.0 (5.0;40.0) n=8	11.98 (10.60) 7.5 (4.6;30.0) n=5	16.04 (6.86) 20.0 (8.1;20.0) n=3

For continuous variables Mean (SD) / Median (Min; Max) / n are presented.

Overall the additional use of hydrocortisone due to non-illness related stress was rather stable over time and between groups except for the newly recruited patients in DC 08/01. One reason for the higher use in these patients may be the fact that more patients in this group were treated with 20-25 mg daily. No classification with regard to severity of the episodes was recorded. There are no apparent differences between treatment groups during Part A of study DC 06/02.

Laboratory findings

No statistically significant or clinically relevant changes were observed in the haematology variables.

Small changes were observed in serum sodium and potassium concentrations. However, no consistent trends to indicate over- or under-substitution were observed.

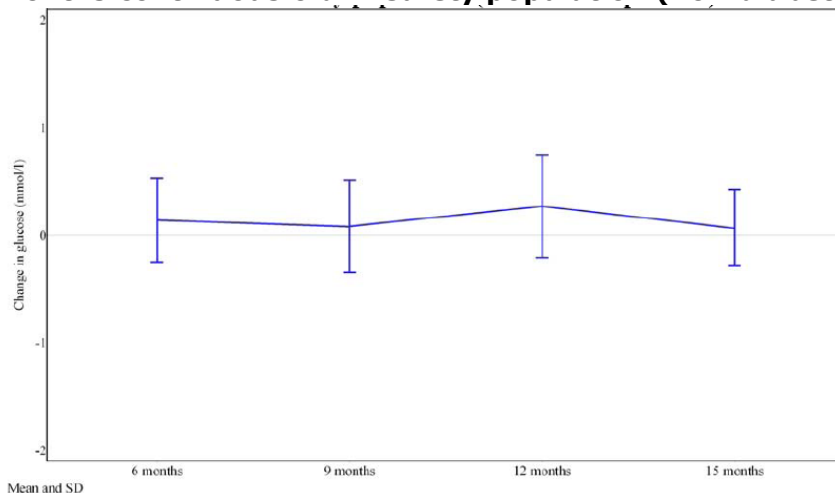
Very small changes were seen in glucose and lipid metabolism when t.i.d treatment was compared with o.d. treatment (Table 14). The changes hardly reached clinical significance and were not consistent with an improvement of the metabolic profile. Patients on o.d. showed a slight decrease in systolic and diastolic blood pressure when compared to t.i.d treatment during Part A of study DC 06/02. These changes may indicate either an improvement of the overall metabolic profile, but may also be an indication of hypocortisolism, thus interpretations are difficult. The observed changes were, however, slow and gradual over a 15 month observation period and there was no indication of a reduction in orthostatic pressure. Thus, the data are not considered indicative of under-substitution.

Table 14 Summary of cardiovascular and metabolic markers, o.d. vs t.i.d. in DC 06/02; Part A

Variable	n	Difference o.d.-t.i.d. Mean (SD)	p-value
HbA1c (%)	57	-0.1 (0.4)	0.0007
S-cholesterol (mmol/l)	51	0.0 (0.4)	0.6729
S-LDL cholesterol (mmol/l)	51	0.0 (0.3)	0.9131
S-HDL cholesterol (mmol/l)	51	-0.1 (0.2)	<0.0001
S-triglycerides (mmol/l)	51	0.2 (0.6)	0.0086
SBP (mm Hg)	60	-5.5 (11.3)	0.0001
DBP (mm Hg)	60	-2.3 (8.0)	0.0343
Heart rate (bpm)	60	2.2 (6.3)	0.0026
BMI (kg/m ²)	60	-0.2 (0.6)	0.0040

No clinically significant changes in glucose, HbA1c or lipids were observed during the long-term follow-up of patients on o.d. as exemplified in Figure 8.

Figure 8 Line graph of change in glucose (mmol/l) from baseline to 6, 9, 12 and 15 months continuous o.d. – safety population (non-diabetic patients)



In patients with DM, HbA1c initially decreased; however, this decrease was not maintained.

Study DC 06/02 included two bone formation markers, osteocalcin and PINP (N-terminal propeptide of type I procollagen), as patients with AI on long-term glucocorticoid replacement therapy are known to have reduced bone mineral density. The mean serum concentration of the bone formation marker PINP increased from baseline to 12 weeks on o.d. treatment while a decrease was observed on t.i.d. treatment (6.1 µg/l; p=0.004 for the difference o.d.- t.i.d.) suggesting increased bone formation with o.d. therapy. No statistically significant change in osteocalcin levels was observed between o.d. and t.i.d. treatment from baseline to 12 weeks.

No changes in either systolic or diastolic blood pressure compared to baseline in study DC 06/02 or start of study DC 08/01 was observed in the 18 month follow-up in study DC 08/01. A statistically significant decrease in body weight and BMI was observed from baseline; however, changes from start of study DC 08/01 did not reach statistical significance.

Safety in special populations

No specific data have been provided. Within the safety population, the frequency of AEs was similar between elderly and non-elderly adults, as well as between males and females and between obese and non-obese patients. Selected safety data was presented for the subgroup of patients with diabetes. These data give no indication that the safety profile of Plenadren is different in this sub-group of patients.

Safety related to drug-drug interactions and other interactions

No drug interaction studies have been conducted with hydrocortisone (Plenadren).

Discontinuation due to AES

Two patients withdrew from the studies due to AE(s); one patient due to an SAE (subarachnoid haemorrhage) and one patient who experienced pyrexia, nasopharyngitis and fatigue (the patient did not specify what AE(s) led to withdrawal). One additional patient has discontinued from study DC 08/01 due to an SAE (death - fall from height).

2.4.10 Discussion on clinical safety

As adrenal insufficiency is a rare disease, the safety data base is small, only 80 patients. Out of these, 68 patients were treated for more than 12 months. The safety data derived from trials DC 06/01 (in healthy volunteers), Part B of DC 06/02 and DC 08/01 (ongoing trial) are considered as supportive.

When o.d. treatment is compared to t.i.d. treatment with regards to AEs, the pattern is rather similar, however, fatigue, gastrointestinal disorders and musculoskeletal disorders are more frequently reported in the o.d. treated group. AEs were more common in the o.d. group especially during the first weeks of treatment. This could be an indication of hypocortisolism when switching from t.i.d. to o.d., especially taking the lower exposure with Plenadren into account. At twelve weeks of treatment, the differences were less pronounced. The pattern of a transient worsening is similar to that seen in the QoL data.

The number of SAEs was rather low. The majority of SAEs were due to infections (gastroenteritis). More SAEs were observed in the Plenadren treated groups. There is no obvious explanation to this discrepancy between groups and the difference may be due to chance. The additional data provided from the long-term follow-up study show a lower rate of SAEs. When compared to published (Hahner et al, 2010; 2011) and unpublished (Forss et al 2011) data the rate of SAEs is within the range observed in a clinical setting.

The Applicant has provided a separate analysis of data on patient reporting intercurrent illness and non-illness related hydrocortisone usage. It appears that the mean number of episodes among patients reporting events was rather similar in the different three-month periods studied, and also between treatments. No data on severity has been provided. The mean duration of the episodes was not different between treatments. Although more patients on Plenadren experienced intercurrent illness episodes, there is no indication that Plenadren is less efficient than t.i.d. in treating these episodes. Furthermore, the pharmacokinetic data indicate that a more stable basal cortisol level (higher through levels) is achieved with Plenadren b.i.d. or t.i.d. than with conventional treatment which is reassuring. Overall the additional doses only constitute about 2-3 % of the total hydrocortisone intake. Taking into account that current treatment in intercurrent illness is largely empirical the SmPC has been amended to include adequate information to allow the prescriber to make an informed decision on whether to recommend the administration of Plenadren twice or three times daily, the addition of immediate

release hydrocortisone together with the Plenadren dose or the administration of immediate release hydrocortisone as single therapy in intercurrent illness, taking into account that treatment recommendations may differ in different European countries. The available data on the use of Plenadren in intercurrent illness is reflected in the SmPC.

2.4.11 Conclusions on clinical safety

The safety profile is not essentially different to that of conventional hydrocortisone. However, fatigue and gastrointestinal disorders were more common during the initial treatment period in the o.d. treated group, as well as musculoskeletal disorders. This indicates a perceived transient hypocortisolism when changing from conventional treatment to Plenadren. The limited data available on dose titration with Plenadren does not answer the question whether these AEs could be avoided by increasing the Plenadren dose or, alternatively, add IR hydrocortisone and it could be hypothesised that a possible increased need for additional doses of hydrocortisone could result in over-substitution of the patients in the long run. However, long-term data does not indicate that the doses are uptitrated over time and adequate warnings are included in the SmPC.

Although the data regarding the use on Plenadren in intercurrent illness are scarce it may be concluded that the use of Plenadren in these situations appears as efficient as the use of conventional therapy. There seems to be no connection between the reported AEs and SAEs that could indicate treatment failure when Plenadren or conventional treatment is used in situations with increased cortisol need. Taking into account that current treatment in intercurrent illness is largely empirical the SmPC has been amended to include adequate information to allow the prescriber to make an informed decision on whether to recommend the administration of Plenadren twice or three times daily, the addition of immediate release hydrocortisone together with the Plenadren dose, as proposed by the SAG (see below), or the administration of immediate release hydrocortisone as single therapy in intercurrent illness taking into account that treatment recommendations may differ in different European countries.

2.4.12 Consultation of Scientific Advisory Group (SAG)

As per CHMP request, a Scientific Advisory Group expert meeting for diabetes/endocrinology reinforced with additional clinical experts was convened on 15 June 2011 to obtain further input on the potential usefulness of Plenadren in the clinical management of Morbus Addison and to provide advice on the list of questions adopted by the CHMP at its April 2001 meeting. The SAG provided the following answers to the questions raised by the Committee:

- 1. It has been shown by the Applicant and from literature references that the AUC observed after cortisol administration is 40-50 % higher when based on immunoassay measurements as compared to a chromatographic method, hence the immunoassay method is not selective for cortisol in plasma samples. Do the SAG have any comments on the immunoassay used for quantification of serum cortisol levels and the consequent inferences from the available PK data relating to efficacy and safety of Plenadren, or the comparison of the modified-release formulation to t.i.d. hydrocortisone?**

The SAG acknowledged the imperfections of the currently available PK data, but disagreed with the PKWP view that the data are uninterpretable. The group was of the view that the PK data submitted provides sufficient information on the relative comparability of the compounds regardless of method used. Information provided by the Applicant indicated that no major unmeasured metabolites of cortisol were present which might have influenced the radioimmunoassay reading differentially. From a clinical viewpoint, chromatography is too

complex to be widely used and clinicians in the EU have significant experience with immunoassay measurements of S-cortisol and a degree of confidence in this method. Moreover, decisions on dosing in the individual patient are taken on clinical grounds based on clinical response (e.g. weight, wellbeing and quality of life) and are not based on measurements of S-cortisol. Therefore, from a clinical perspective, the SAG considered the currently available PK data sufficient and the implications of the inadequate precision of the PK profile not clinically meaningful.

2. The available data indicate a lower exposure of Plenadren in the latter part of the day compared to the perceived physiological profile, and compared to t.i.d. hydrocortisone. When Plenadren was compared to conventional therapy events consistent with under-substitution (e.g. fatigue) were reported more often in the Plenadren group and overall there was a higher reporting of AEs when changing from conventional to o.d. treatment.

a. The SAG is asked to reflect on the PK profile of Plenadren and the consequences for its potential use in clinical practice. In particular, do the SAG foresee a risk of hypocortisolism if Plenadren is used as o.d. treatment in clinical practice?

No. The SAG noted that hypocortisolaemia is not the same as hypocortisolism, and that transient low circulating levels of cortisol do not necessarily indicate lack of physiological effect. The SAG therefore felt that there is little identifiable risk associated with potential hypocortisolism late in the day, and this is not of concern. On the contrary, the SAG members emphasised the fact that cortisol levels should be low in the evening to minimise the risk of short-term side effects such as insomnia as well as other long-term side effects such as cardiovascular complications and osteoporosis.

b. There was a higher reporting of AEs when changing from conventional to o.d. treatment during the first 4-8 weeks of treatment. However, no difference between groups was seen during the subsequent 3-month periods of o.d. treatment with respect to incidence of AEs. Could this reflect a relative hypocortisolism as a result of a potential previous overexposure? Would this constitute a problem in clinical practice?

No. The SAG was of the view that a potential relative hypocortisolism would not constitute a problem in clinical practice.

c. If undersubstitution compared to a conventional treatment regimen is an issue, it could be assumed that an increase in the once daily dose of Plenadren or use of another cortisone is needed to overcome the cortisol shortage in the latter half of the day, leading to higher peaks of cortisol in the morning. Does the SAG consider this to represent a potential risk of oversubstitution of the patients and thereby a risk of long term complications?

No. Since hypocortisolism late in the day was not seen as an issue in clinical practice (see 2b), there would be no need for adjustment with an increase of the morning dose. Consequently, the SAG did not consider over-substitution a potential risk.

3. A correct dosing in the case of intercurrent illness is of utmost importance in the treatment of patients with adrenal insufficiency. The Applicant's proposal is to double the daily dose giving a second dose of Plenadren 8 ± 2 hours after the morning dose in the case of milder clinical conditions. In more serious conditions, and when the expected clinical response is not achieved when doubling the dose, the daily dose

should be tripled giving three daily doses of Plenadren with 8 hours intervals. Do you consider that the evidence-base to justify this proposal is adequate? If not, would it be more appropriate to recommend the use of immediate release hydrocortisone in situations associated with an increased demand?

The SAG noted that intercurrent illness is a serious complication of adrenal insufficiency, and potentially life threatening. For this reason, severe episodes require hospital admission and steroid supplementation. The present discussion therefore related to less severe, self-treated stressful situations. The evidence-base for the Applicant's proposal to double or triple the dose of Plenadren in this situation was not considered fully adequate at present and the SAG was of the view that more PK data are needed in patients undergoing stressful situations such as mild and severe intercurrent illness. From a clinical viewpoint, the experts agreed that the most important consideration is to avoid underexposure in patients in acute situations while potential over-exposure was not considered an issue in patients with intercurrent illness. Broadly the SAG agreed that the limited data provided are reassuring, however, there was concern whether in the event of illness patients would be adequately treated by applying the proposed scheme to double or triple the dose of Plenadren, in particular in comparison with the present use of immediately resorbed hydrocortisone. In situations of mild illness it might be sufficient to double the dose of Plenadren, but in severe illness the SAG was of the view that a switch to the IR-formulation may be necessary. The SAG agreed that a clinically safe approach might be to continue treatment with Plenadren and to top-up with IR hydrocortisone, rather than a complete switch to IR hydrocortisone. The SAG expressed the view that clear guidance in this regard should be included in the SmPC. The experts agreed that further data would be needed before the proposal not to use IR hydrocortisone in times of crises could be agreed.

- 4. Are you of the opinion that Plenaren being dosed once daily, would be useful in the individualised treatment of adults with adrenal insufficiency? If yes, and in line with the responses to previous questions, would more clinical data be necessary to permit a safe and efficacious use of Plenadren in clinical practice? If yes, what kind of data should be available?**

The SAG agreed that, based on the currently available data, and provided that an adequate risk management plan is in place, Plenadren being dosed once daily would be a useful additional therapeutic option in some patients with adrenal insufficiency in clinical practice. Further, the SAG supported the proposed post-marketing pharmacovigilance activities (study SWE-DUS and registry EU-AIR). However, the group agreed that further PK data in patients with intercurrent illness should be requested in order to generate further guidance on how best to handle patients on Plenadren in this situation.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

Risk Management Plan

The Applicant submitted a risk management plan, which included a risk minimisation plan.

The safety concerns specified by the Applicant include 1 identified risk; cortisol deficiency-related symptoms after change from immediate release hydrocortisone, and 4 potential risks; glucocorticoid under-replacement, glucocorticoid over-replacement, drug and drug interactions and off-label use in children and adults. Use in elderly subjects, hepatic impairment, renal impairment, pregnant and lactating women, paediatric subjects, gastrointestinal emptying or motility disease or disorder and mortality, long terms safety and mortality are addressed as missing information.

Table 15 Summary of the EU Risk Management Plan

Identified risk	Pharmacovigilance activities	Risk minimisation activities
Cortisol deficiency-related symptoms after change from immediate release hydrocortisone	<ul style="list-style-type: none"> • Routine Pharmacovigilance • Review of incidence and outcome of cortisol deficiency related symptoms from a large registry study. 	<p>Routine risk minimisation activities</p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the section:</p> <p>4.2 Posology and method of administration</p> <p>4.8 Undesirable effects</p>
Potential risk	Pharmacovigilance activities	Risk minimisation activities
Under – replacement	<ul style="list-style-type: none"> • Routine Pharmacovigilance • Review of incidence and outcome of infections, intercurrent illness and cortisol deficiency-related symptoms from a large registry study. 	<p>Routine risk minimisation activities</p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section</p> <p>4.2 Posology and method of administration</p> <p>4.4 Special warnings and special precautions for use.</p> <p>4.5 Interaction with other medicinal products and other forms of interaction</p> <p>4.6 Fertility, pregnancy and lactation</p>
Over-replacement	<ul style="list-style-type: none"> • Routine Pharmacovigilance • Review of incidence and outcome of infections, intercurrent illness and cortisol deficiency-related symptoms from a large registry study. 	<p>Routine risk minimisation</p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section</p> <p>4.2 Posology and method of administration in the SmPC</p>
Off-label use	<ul style="list-style-type: none"> • Routine Pharmacovigilance • Drug utilisation study to monitor the off-label use in children and adults • Review of incidence off-label use in children and off-label use during intercurrent illness from a large registry study. 	<p>Routine risk minimisation activities</p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section</p> <p>4.1 Therapeutic indications</p>
Pregnancy and lactation	<ul style="list-style-type: none"> • Routine Pharmacovigilance 	<p>Routine risk minimisation activities</p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section</p>

<p>Potential Drug interactions: Drug-drug interaction with CYP3A4 inducers and inhibitors</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • To review information on the drug interaction with Plenadren in a large registry study 	<p><u>Routine risk minimisation activities SmPC</u></p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section 4.5 Interaction with other medicinal products and other forms of interaction</p>
<p>Missing information</p>	<p>Pharmacovigilance activities</p>	<p>Risk minimisation activities</p>
<p>Paediatric safety</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • Drug utilisation study to monitor off-label use in children and adolescents. • To monitor off-label use in children and adolescents with Plenadren in a large registry study 	<p><u>Routine risk minimisation activities SmPC</u></p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section 4.2 Posology and method of administration</p>
<p>Renal impairment</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • To review information on the safety of long term treatment with Plenadren in patient subgroups in a large registry study 	<p><u>Routine risk minimisation activities SmPC</u></p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section 4.2 Posology and method of administration</p>
<p>Hepatic impairment</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • To review information on the safety of long term treatment with Plenadren in patient subgroups in a large registry study 	<p><u>Routine risk minimisation activities SmPC</u></p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section 4.2 Posology and method of administration</p>
<p>Elderly</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • To review information on the safety of long term treatment with Plenadren in patient subgroups in a large registry study 	<p><u>Routine risk minimisation activities SmPC</u></p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section 4.2 Posology and method of administration</p>
<p>Gastrointestinal emptying or motility disease or disorder</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • To review information on the safety of long term treatment with Plenadren in patient subgroups in a large registry study 	<p><u>Routine risk minimisation activities SmPC</u></p> <ul style="list-style-type: none"> • SmPC <p>Appropriate information have been incorporated in the SmPC in section 4.4 Special warnings and special precautions for use</p>
<p>Long term safety</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • Review of long term safety outcome from a large registry study 	<p>Not applicable</p>
<p>Mortality</p>	<ul style="list-style-type: none"> • Routine Pharmacovigilance • Review of incidence and 	<p><u>Routine risk minimisation activities</u></p>

outcome of mortality from a large registry study

- SmPC
Appropriate information have been incorporated in the section:
4.4 Special warnings and precautions for use
-

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
EU-AIR: A prospective multicentre, European registry of patients with chronic adrenal insufficiency.	Progress reports to be provided on a 6-monthly basis as part of the PSURs
SWE-DUS: A Swedish, retrospective, study, evaluating the pattern of Plenadren use from Swedish quality registries	Progress reports to be provided on a yearly basis as part of the PSURs

No additional risk minimisation activities were required beyond those included in the product information.

2.6 User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet 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. In conclusion, the user test is considered acceptable.

3 Benefit-Risk Balance

Benefits

Beneficial effects

Adrenal insufficiency, either primary as a result of a disease in the adrenal cortex or secondary due to an underlying hypothalamic-pituitary disorder, has to be life-long treated with cortisol replacement. Current treatment with twice or three times daily hydrocortisone is an attempt to mimic the physiological diurnal cortisol profile. There are data that indicate that this treatment may result in an over exposure to cortisol resulting in increased morbidity and mortality in this patient group. There is also data indicating an excess mortality in situations of increased cortisol need such as in severe intercurrent illness.

The current application concerns a new formulation, Plenadren, designed to better mimic the physiological profile and allow once daily dosing in order to increase patients compliance. The rationale

for this development is that a more physiological profile of the replacement therapy may transform into a more favourable metabolic profile which eventually could result in a decrease in morbidity and mortality in the target population while still providing a sufficient cortisol replacement with a once daily dosing regimen.

The pharmacokinetic data are considered sufficiently reliable for characterisation of dose proportionality 5 vs 20 mg, food effect and comparison of shape of concentration time profile and relative PK parameters for Plenadren q.d. vs IR t.i.d (three times a day).

Plenadren exhibits a high cortisol concentration peak in the morning and a slow decline during the afternoon with once daily treatment, thereby partly mimicking the physiological profile.

The use of b.i.d. (twice a day) or t.i.d treatment is known to decrease patient's compliance. The patient's preference and the tolerability of the new formulation were evaluated via questionnaires and QoL assessment throughout the study programme. The results of these analyses have to be interpreted with caution due to the open design of the studies. However, the QoL data indicated a worsening of the patient's well-being during the first four weeks after changing from conventional to treatment to Plenadren, but not during the following treatment period. No other significant differences in QoL or tolerability were observed when Plenadren was compared to conventional treatment. However, patient's preference lay with Plenadren. Furthermore, only five patients out of 80 patients chose to go back to conventional therapy due to impaired well-being.

Uncertainty in the knowledge about the beneficial effects

As over-substitution is one of the identified problems with the current replacement therapy in adrenal insufficiency, the lower exposure achieved with Plenadren may be of benefit. However, due to the relatively short treatment periods, the data provided in the phase II/III study were not able to support an improved metabolic profile of Plenadren compared to conventional treatment. However, over the three month comparative period, a slight decrease in systolic and diastolic blood pressure as well as a slight decrease in body weight was observed for Plenadren when compared to t.i.d. treatment.

Risks

Unfavourable effects

The proposed product information states that no dose adjustment is needed when changing from conventional to the new formulation. When Plenadren was compared to conventional therapy, fatigue was reported more often in the Plenadren group and overall there was a higher reporting of AEs when changing from conventional to o.d. (once daily) treatment during the first 4 weeks of treatment. However, no difference between groups was seen during week 8-12 with respect to incidence of AEs. This may indicate that, when changing between therapies is done on a milligram basis, the exposure will be too low in some patients. Further to this, more patients needed additional doses when on Plenadren compared to conventional treatment. This may indicate a relative under-substitution when changing from t.i.d. to o.d. dosing. Under-substitution is a serious problem which could result in over-substitution due to the need for additional doses, which in turn run could lead to serious metabolic consequences in the long run. However, in the ongoing study DC 08/01, in which titrations have been made based on clinical judgement, there was a decreased use of extra doses over time. The majority of patients that have had their doses changed in this study have indeed decreased the dose. Further to this the data indicate that patients who were not feeling well on Plenadren rather choose to go back to conventional therapy than to increase the dose. The SAG meeting did not consider that the low exposure late in the day would constitute a problem in clinical practice.

Another safety aspect of the new formulation which has to be addressed is the adaptation of the dosage to minor illnesses when increased cortisol doses are needed. The clinical evaluation of the additional use of Plenadren in intercurrent illness does not indicate that Plenadren is less efficient than conventional treatment when taken in these situations based on the observation that the length of the episodes was similar for both treatments as well as the mean dose used for each episode. The pharmacokinetic data further indicate that the proposed posology for the use of Plenadren in intercurrent illness would ensure a more stable increase in basal cortisol levels (higher trough levels) than with conventional therapy.

Taking into account that current treatment in intercurrent illness is largely empirical the SmPC has been amended to include adequate information to allow the prescriber to make an informed decision on whether to recommend the administration of Plenadren twice or three times daily, the addition of immediate release hydrocortisone together with the Plenadren dose or the administration of immediate release hydrocortisone as single therapy in intercurrent illness, taking into account that treatment recommendations may differ in different European countries. The available data on the use of Plenadren in intercurrent illness is reflected in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

The safety data base is limited with only 80 patients having been treated with Plenadren. A majority of these patients (68) have, however, been treated for more than one year.

Since the controlled part of the clinical programme did not allow up-titration of the dose in case of lack of efficacy, there is no clinical data available on whether increasing the dose would be effective in overcoming the symptoms of under-substitution (i.e. fatigue) or whether increasing the dose would lead to over-replacement which in turn would negatively affect the safety profile. The data from the long-term follow up study; however, are reassuring since the majority of patients maintained their dose unchanged and thus achieved a lower exposure. Of the patients who did change their dose, more patients had their dose decreased than increased. The additional dosing, both with regards to intercurrent illness and physical or emotional stress, remained stable over the reported 18 months of the study.

Patients with disturbances in gastric motility were excluded from the clinical programme. It is therefore unknown whether such patients can be safely treated with Plenadren. There is also a lack of data regarding the use of Plenadren in situations with chronic diarrhoea. These issues have been addressed in the SmPC.

Balance

Importance of favourable and unfavourable effects

The proposed beneficial effect of Plenadren compared to conventional treatment is that a more physiological profile of the replacement therapy may transform into a more favourable metabolic profile which eventually could result in a decrease in morbidity and mortality in the target population while still providing a sufficient cortisol replacement. Although the clinical data is insufficient to make any claims on improvements with regards to metabolic effects with Plenadren, a once daily dosing regimen could however be of benefit in the context of convenience and patient compliance. The complex glucocorticoid system is hard to mimic during oral replacement therapy and finding the adequate dose for each patient is challenging due to the lack of a serum marker of the biological activity of cortisol. The multiple dosing may be associated with an increased risk of non-compliance, and for some patients a once daily dosing is expected to be beneficial. This was also reflected in a

higher patient's preference, even though no significant improvement in QoL could be observed. A high patient's preference is an important aspect since this is a treatment where missed doses may quickly lead to serious consequences to the patient.

As mentioned above, the titration of the cortisone dose in clinical practice is always performed on an individual basis. To allow an adequate clinical use, a new formulation needs to be sufficiently well characterised, but there is no absolute need to be similar to other formulations. This would also be sufficient, considering the legal basis of the application which does not call for bioequivalence to be shown.

Thus, characterisation of the shape of the concentration time profile of the new formulation in comparison to the established t.i.d (three times a day). treatment is considered important. Although the analytical methods used are nonspecific, the pharmacokinetic data are considered sufficiently reliable for this comparison.

In the treatment of adrenal insufficiency, there is both the risk of under- and over-substitution. The most important and immediate risk with cortisol replacement therapy is the risk of under-substitution since this would affect the patient's ability to cope in everyday life. In situations of increased need of cortisol, too low doses may be life-threatening since the patient may develop an Addison crisis. If the replacement dose is too high, the patient is at risk of all the known and well described adverse effects of high cortisol doses. Epidemiological data suggest that also modestly increased doses may cause negative metabolic effects.

The PK data indicate a lower exposure of Plenadren compared to conventional treatment, especially at the end of the day, which is in accordance with the intention of this new formulation. However, clinical data indicate that, in some patients, the decrease in overall cortisol exposure may result in an initial, possibly relative, transient under-substitution when patients are switched on a milligram basis. However, in clinical practise this is not considered to be a major problem, which was supported by the SAG. Concerns have been raised that possible dose increases to overcome under-substitution in the afternoon may lead to over-substitution during the earlier hours of the day which in turn may negatively affect the safety profile. However, neither data from the phase II/III study nor from the long-term follow up study indicate an increase in dose over time.

Furthermore, with knowledge on the shape of the concentration-time profile, treatment could be individualised, which in some cases may be to add additional low doses of immediate release hydrocortisone in the afternoon. Considering the lower bioavailability of Plenadren, this may be done with no or minor increase in total exposure compared to t.i.d. treatment.

Benefit-risk balance

In theory, a lower cortisol exposure in the late afternoon/ night could be beneficial with respect to long term safety and well being. Long-term beneficial effects of Plenadren in terms of a better metabolic profile compared to conventional treatment has not yet been shown. However, showing such a beneficial effect would most likely require long term treatment (i.e. several years). Further, a once daily dosing regimen could be a beneficial alternative to currently available therapy for some patients which is also reflected by the patient's preference.

The PK profile is considered as satisfactorily characterised and admits the use of Plendaren in clinical practice.

Due to the PK profile of Plenadren there may be a risk of, at least temporarily, under substitution in the afternoon in some patients, particularly in stressful situations. This could be overcome by temporarily combining Plenadren with IR hydrocortisone. During intercurrent illness Plenadren may be

administered twice or three times daily, may be combined with IR hydrocortisone or IR hydrocortisone may be administered as single therapy alone. The clinical data do not raise concerns regarding increased exposure over time in terms of dose increase.

Thus, the risks are considered as manageable and are outweighed by the benefits.

Discussion on the benefit-risk balance

Following the assessment of all data on quality, safety and efficacy provided as part of the present MAA, and taking the SAG advice into account, the CHMP concluded that the benefit/risk balance for Plenadren (hydrocortisone) is positive for the following indication:

“Treatment of adrenal insufficiency in adults.”

4 Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Plenadren in the treatment of adrenal insufficiency in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2.4 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached at the request of the EMA.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
EU-AIR: A prospective multicentre, European registry of patients with chronic adrenal insufficiency.	Progress reports to be provided on a 6-monthly basis as part of the PSURs
SWE-DUS: A Swedish, retrospective, study, evaluating the pattern of Plenadren use from Swedish quality registries	Progress reports to be provided on a yearly basis as part of the PSURs

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.