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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Efmody (hydrocortisone)
Treatment of congenital adrenal hyperplasia
EU/3/05/296

Sponsor: Diurnal Europe B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Hydrocortisone
Other name(s)	-
International Non-Proprietary Name	Hydrocortisone
Tradename	Efmody
Orphan condition	Treatment of congenital adrenal hyperplasia
Sponsor's details:	Diurnal Europe B.V. Van Heuven Goedhartlaan 935 A 1181 LD Amstelveen Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Professor Richard JM Ross, University of Sheffield
COMP opinion date	15 June 2005
EC decision date	27 July 2005
EC registration number	EU/3/05/296
Post-designation procedural history	
Transfer of sponsorship	Transfer from Professor Richard JM Ross, University of Sheffield to Phoqus Pharmaceuticals Limited – EC decision of 18 December 2006
	2nd transfer from Phoqus Pharmaceuticals Limited to Diurnal Limited – EC decision of 11 February 2009
	3rd transfer from Diurnal Limited to Diurnal Europe B.V. – EC decision of 12 February 2019
Correction of the active substance name	Active substance corrected from Hydrocortisone (modified release tablet) to Hydrocortisone - EC corrigendum C(2020)1245 of 26 February 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	J. L. Hillege / K. Dunder
Applicant	Diurnal Limited
Application submission date	12 December 2019
Procedure start date	23 March 2020
Procedure number	EMA/H/C/005105
Invented name	Efmody
Proposed therapeutic indication	Treatment of congenital adrenal hyperplasia (CAH) in patients aged 12 years and over. Further information on Efmody can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Efmody
CHMP opinion date	25 March 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	E. J. Rook / L. Gaidadzi
Sponsor's report submission	14 May 2020

COMP discussion and adoption of list of questions	16-18 February 2021
Oral explanation	14 April 2021
Sponsor's removal request	15 April 2021

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2005 designation was based on the following grounds:

Whereas the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- congenital adrenal hyperplasia (hereinafter referred to as "the condition") was estimated to be affecting not more than 1 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening in particular due to the development of addisonian crisis and virilisation of the female, precocious puberty, short stature, and infertility in case of inadequate treatment;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that hydrocortisone (modified release tablet) may be of significant benefit to those affected by the condition.

the COMP recommends the designation of this medicinal product, containing hydrocortisone (modified release tablet), as an orphan medicinal product for the orphan indication: treatment of congenital adrenal hyperplasia.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Congenital adrenal hyperplasia (CAH) is a rare genetic disorder of steroidogenesis. In its classic form, there is a deficiency of the enzyme 21-hydroxylase. Lack of 21-hydroxylase causes cortisol deficiency and resultant compensatory elevated pituitary adrenocorticotropic hormone (ACTH), which drives the overproduction of 17-hydroxyprogesteron (17-OHP) and adrenal androgens and causes adrenal hyperplasia and adrenal nodules as long-term manifestation. Patients with CAH suffer from adrenal insufficiency (AI) and androgen excess. Adrenal insufficiency (AI) may cause life threatening adrenal crises (Rushworth, Torpy, and Falhammar 2019), while androgen excess causes atypical genitalia in female neonates, precocious puberty and short stature, and in adulthood, virilization of women and

infertility in both sexes (Merke and Auchus 2020). In the classic form, patients also have a shortage of aldosterone production, leading to salt wasting.

The approved therapeutic indication "treatment of congenital adrenal hyperplasia (CAH) in patients aged 12 years and over" falls within the scope of the designated orphan condition "treatment of congenital adrenal hyperplasia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

Since designation there has been no new products authorised specifically for the treatment of CAH. Studies since designation have confirmed the morbidity and risk of early mortality associated with the condition (Falhammar et al. 2015; Jenkins-Jones et al. 2018; Sarafoglou et al. 2014; Bonfig et al. 2016; Arlt et al. 2010). Adolescents share all the risk factors and risk of co-morbidities with adults, but also have the added risk that growth can be compromised either by excess glucocorticoid replacement or by inadequate replacement leading to disease over-activity (Speiser et al. 2018; Sarafoglou et al. 2014). This is despite a general trend towards lower doses of glucocorticoid over the last 30 years although these remain higher than those recommended for adrenal replacement therapy (Sarafoglou et al. 2014).

The condition remains chronically debilitating and life threatening.

Number of people affected or at risk

At the time of original designation for Efmody the prevalence was estimated to be less than 1:14,000 and agreed by COMP to be less than 1:10,000. This submission updates those estimates with literature published since time of designation.

Based on all available sources which includes one additional publication, the sponsor believes that a reasonable estimate is that CAH has a birth prevalence of ~1:12,000. Birth prevalence is the highest prevalence of this congenital disease due firstly to higher than average mortality, and secondly to a lack of effective treatment before 1950 which means that there are very few patients older than 65 years of age. The sponsor believes that a prevalence of 1:12,000 is a generous estimate of the prevalence in Europe, equating to CAH affecting 0.8:10,000 people within the European Union (EU).

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Treatments authorised in the EU for replacement therapy in CAH include multiple nationally authorised generic hydrocortisone therapies in 10mg and 20mg dose strengths, nationally authorised cortisone acetate preparations, nationally authorised prednisolone and methylprednisolone preparations and nationally authorised preparations of dexamethasone.

The current accepted international guidelines for management and treatment of CAH were developed by the (US) Endocrine Society in conjunction with the European Society of Endocrinology and European Society for Paediatric Endocrinology (Speiser et al. 2018). In growing patients, these guidelines recommend therapy with hydrocortisone, and recommend against use of long-acting potent glucocorticoid preparations, because of the risk of growth suppression with these preparations.

In adults the preference is for hydrocortisone with long-acting glucocorticoid preparations such as prednisolone, prednisone or dexamethasone as alternatives (Speiser et al. 2018). Recent publications have advised caution with dexamethasone due to its association with Cushingoid adverse events, poor bone mineral density and potential weight gain (Auchus and Arlt 2013; Whittle and Falhammar 2019), and prednisolone has also been associated with reduced bone density (Riehl et al. 2019).

In stress situations (e.g. surgery or infections), additional doses of glucocorticoids maybe needed to prevent adrenal crisis, in addition to chronic treatment.

Classic CAH patients also commonly require treatment with fludrocortisone at diagnosis in the new-born period. The need for continuing mineralocorticoids should be assessed based on plasma renin activity and blood pressure. Sodium chloride supplements are often needed in infancy.

The non-classic form of CAH is not usually treated with complete replacement therapy (only supplementation in stress situations).

Significant benefit

For this maintenance procedure the most relevant comparator for the assessment of significant benefit is the standard therapy with immediate release hydrocortisones and other longer-acting glucocorticoids like prednisolone.

With regards to Plenadren, a long-acting hydrocortisone authorised for treatment of adrenal insufficiency (AI), the CHMP similarity assessment report concluded that the therapeutic indications of Plenadren and Efmody do not overlap. Therefore, this product should not be considered as a satisfactory method of treatment of CAH. The same in principle applies to the centrally authorised Alkindi (hydrocortisone granules in capsules for opening), which is authorised for paediatric AI from birth to <18 years. Cortisol has a distinct circadian rhythm with a nadir at night on going to sleep, rising in the early hours of the morning from 2-4 am, peaking on waking and declining over the day to low concentrations in the evening (Debono et al. 2009). Treatment of CAH aims to replace the adrenal glucocorticoid cortisol, and where necessary the mineralocorticoid aldosterone, and so prevent the ACTH-driven androgen excess. The challenge facing the physician is balancing the glucocorticoid dose to avoid the complications of both glucocorticoid excess and glucocorticoid deficiency, particularly life-threatening adrenal crises. Current glucocorticoids used in the treatment of CAH such as hydrocortisone, cortisone acetate, prednisolone, prednisone, and dexamethasone, may not be optimal to reproduce the natural overnight rise in cortisol (Debono et al. 2015). In two large cohort studies disease control is only achieved in approximately 40% of patients with the uncontrolled patients either over or under treated with glucocorticoids (Arlt et al. 2010; Finkielstain et al. 2012).

The product's invented name is Efmody, however the company's internal names previously were Chronocort or Cirkrono, so these names may also appear in the following section of the document.

Efmody is a modified-release formulation of hydrocortisone that was designed to treat CAH more effectively than standard glucocorticoids treatment, with hydrocortisone levels that are more similar to endogenous daily cortisol rhythm under conditions without stress that would require extra hydrocortisone. The product has to be taken twice daily, before sleeping and in the morning.

The marketing authorisation application was based on the following clinical studies.

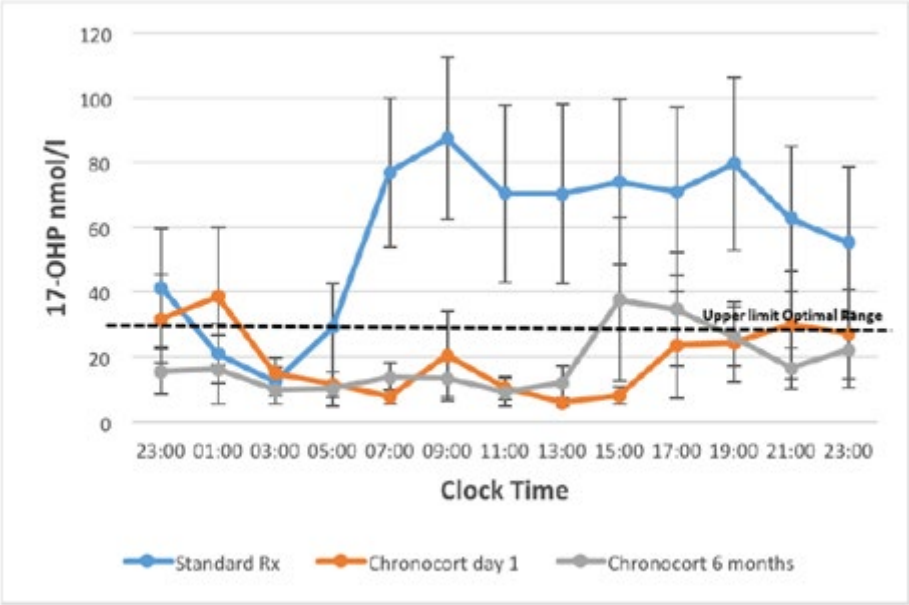
A phase 2 study (DIUR-003) was designed to examine the disease biomarker response to treatment both in the short-term (after 2 days dosing) and after 6 months of treatment in order to inform on the dose and study design for the subsequent phase 3 study. In 16 participants with 21 hydroxylase deficiency compared baseline androgens on standard therapy with Efmody pharmacokinetics and androgen control (17-OHP and androstenedione [A4]) at 48 hrs and 6 months (Figure 1). Patients were switched from their standard treatment with glucocorticoids and converted to Efmody oral capsules given twice daily (20mg at night and 10mg in the morning) at 30 mg/day for 6 days (part A). Patients were then followed for 6 months with dose adjustments at 2 weeks and 2 and 4 months according to androgen levels (part B).

Figure 1. DIUR-003 study schematic

Reference: DIUR-003 CSR

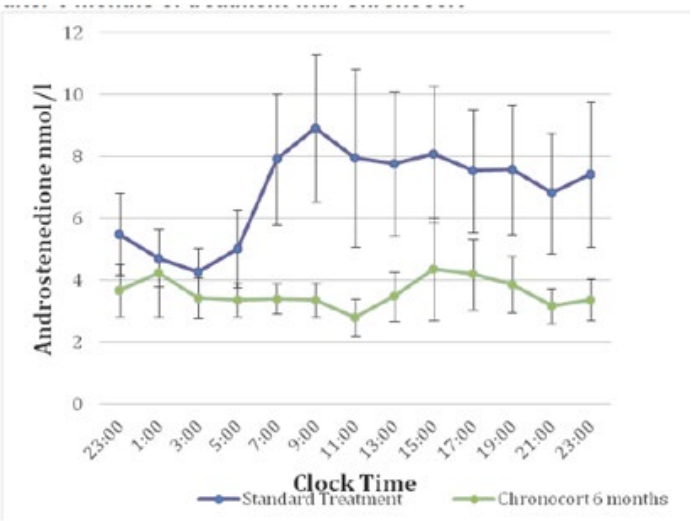
On standard therapy at baseline, the mean 17-OHP level was above the optimal range (36 nmol/l) for most of the day and only dipped down when the subjects were given a dose of steroid last thing at night, but then rose from 0300h as the pituitary adrenal axis became active. On Efmody at 6 months, all but one of the mean 17-OHP levels were within the optimal range (9-36 nmol/l, see Figure 2).

Figure 2. Mean 17-OHP levels during standard therapy at baseline, after the first administration of Efmody (Day 1) and following 6 months of continued Efmody treatment (mean ± SEM).



On standard treatment at baseline the mean A4 level is above the upper limit of the normal range for both men and women over most of the day, whilst after 6 months of treatment with Efmody, the A4 is within the normal range throughout the 24 hours (Figure 3).

Figure 3. Mean and SEM A4 level on standard treatment at baseline and after 6 months of treatment with Efmody

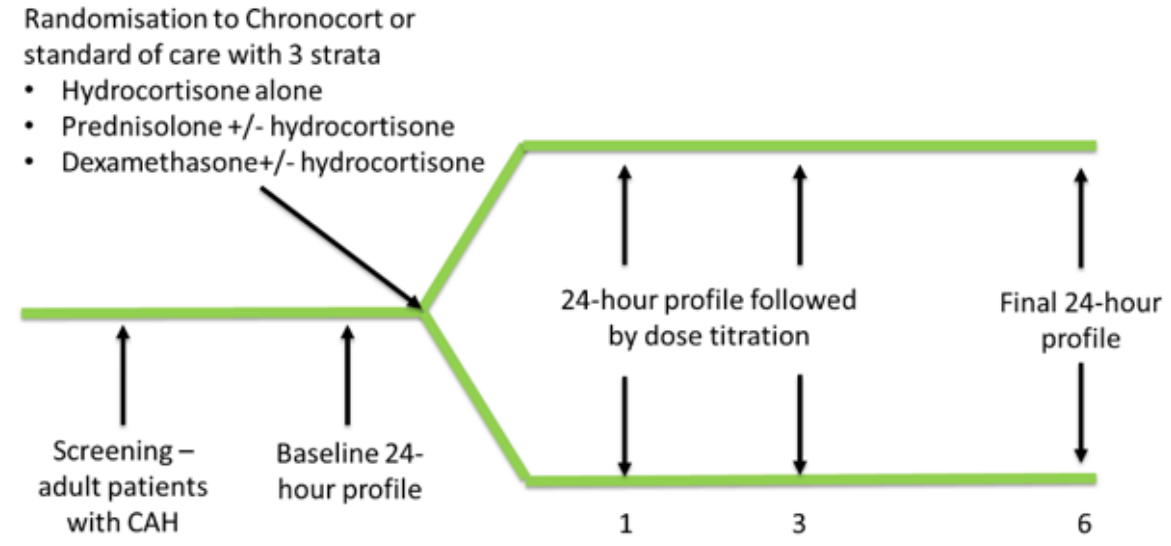


After 6 months of treatment, 15 of 16 patients had a 09.00 hours 17-OHP level within the optimal range. For the standard therapy group this was 5 of 16 patients.

As mentioned by the CHMP Rapporteurs (see EPAR), the study design is considered adequate to provide the proof of concept. It is not considered sufficient to provide evidence to confirm the hypothesis that Efmody can provide superior androgen control compared to standard treatment since the study did not contain a control arm. Neither was standard treatment optimised at baseline.

A Phase 3 study, DIUR-005: 122 participants with classic 21 hydroxylase deficiency, were randomised to Efmody or continuation of standard care with blinded titration of dose based on 24-hour inpatient hormone. Better disease control was achieved in both treatment arms from baseline to Week 24, as measured by 17-OHP (Figure 4).

Figure 4. FDIUR-005 6-month study schematic



Reference: DIUR-005 CSR

Patients from Study DIUR-003 and DIUR-005 could enter the open-label extension study DIUR-006 where they could be treated with Efmody for another 12 months. The main objective of this study was to evaluate long-term Safety.

Efmody is claimed to present a more optimal delivery of hydrocortisone with a dosage form that has a delayed release and sustained absorption. With this drug delivery modality, dosing the formulation at night (and early in the morning) would lead to a profile of hydrocortisone levels more similar to endogenous daily cortisol rhythm, than could be achieved with standard glucocorticoids treatments.

In line with CHMP guidance (COMP-15893-2009) protocol assistance has been sought for justification of significant benefit on three occasions. In the initial protocol assistance in 2007, COMP stated that "significant benefit could be supported if Efmody would be superior to conventional glucocorticoid treatment in obtaining a normal diurnal cortisol rhythm resulting in 17-OHP levels in the optimal range at a lower/similar daily glucocorticoid dose than using conventional therapy, thereby preventing or reducing the risk of glucocorticoid side effects".

In 2014, COMP further clarified this position stating that "corticosteroid treatment of patients with CAH has dual roles: to substitute for the deficient production and secretion of cortisol and to suppress the overproduction of androgenic precursors from the adrenal glands. Achieving both of these goals at the same time is often difficult – the patient is either given enough glucocorticoids to suppress androgens (resulting in long-term side effects of glucocorticoid excess) or balanced glucocorticoid doses just enough to substitute for the missing cortisol – which in most cases is too little to suppress androgens. Consequently, in adult patients, virilisation and infertility (due to under-treatment) or cushingoid features (secondary to over- treatment) are common. In light of this, COMP stated that if a more physiological corticosteroid replacement therapy be accomplished using Efmody while controlling excess androgen levels, thus reducing/eliminating the risk for corticosteroid overtreatment, COMP

would consider this as a significant benefit, although the evaluation would need to take into consideration the most recent therapeutic alternatives".

The discussion of significant benefit was revisited in 2019 when COMP's position evolved to state that, "it can be said that even if Efmody mimics more closely the level of cortisol in the body, the applicant has not yet demonstrated convincingly how this will translate into a patient relevant benefit, and that significant benefit would need to be demonstrated with clinical data showing improved efficacy, improved safety or major contribution to patient care".

The sponsor considers that Efmody has shown significant benefit in the clinical programme based on improvements seen in the diurnal rhythm. The pharmacokinetic profile of Efmody provides a diurnal cortisol rhythm that replicates the natural circadian rhythm of cortisol providing an overnight rise in cortisol levels to peak on waking similar to that seen in healthy subjects under physiological conditions. This is superior to the findings with both immediate release hydrocortisone that fail to replicate the physiological early morning peak of cortisol (see above).

The sponsor claims that Efmody maintains better control of the androgen precursor, 17-OHP, on the glucocorticoid dose recommended for adrenal replacement therapy, and lower than that reported in the published cohort studies of CAH.

However, in the pivotal study DIUR 005, Efmody failed to show statistically significant superiority to the active control arm of standard GC therapy including immediate release hydrocortisone, for primary and secondary endpoints. Therefore, the argument of improved disease control needs further clarification, in order to assess the clinical significance of the improvement observed.

The sponsor claims that Efmody therapy is associated with evidence of improved fertility with restoration of menstrual cycles. Three pregnancies in females on Efmody, improvement in sperm quality and four partner pregnancies of male study participants were observed. However, in order to further assess this benefit, the sponsor would need to contextualise these outcomes vis-à-vis population on standard of care.

The sponsor argues also that Efmody therapy is not associated with weight gain or a decrease in bone mineral density, which his typically observed for other GC therapies. The sponsor should provide further indirect comparison supported by data for this claim to be treated seriously.

The sponsor also explores the argument of major contribution to patient care due to potentially improved treatment compliance, monitoring and convenience. Efmody therapy provides a twice daily treatment regimen obviating the need for either daytime dosing, or thrice or four times daily dosing, or a reverse circadian pattern of dosing. Efmody reduces the fluctuations (amplitude) in the androgen precursor, 17-OHP, a sample taken in the clinic at approximately 0900 and 1300h after dosing (0600-0800) can be used to titrate therapy that provides an easy to deliver, rational monitoring regimen. However, no treatment burden assessment has been provided which would preferably be supported by an adequate patient reported outcome measure. Efmody therapy had no negative impact on health-related quality of life (HRQoL) when measured using generic questionnaires EQ-5D and MAF. This merely supports comparability of Efmody to the standard of care and cannot be treated as major contribution to patient care.

Finally, the safety profile of Efmody does not differ substantially from the known published profile of other established hydrocortisone preparations and is associated with a reduced incidence of life-threatening adrenal crisis and the use of sick day dosing compared to standard therapy according to the sponsor. This is in contrast to the other modified release hydrocortisone, Plenadren, where a higher

risk of adrenal insufficiency symptoms was seen at time of switching therapy from standard glucocorticoid therapy (DIUR-005/DIUR-006 and Plenadren EPAR).

The assumption of significant benefit needs further elaboration and clarification from the sponsor's side. The COMP will require a clarification of the clinical relevance of disease control improvement observed in the context of lack of superiority. Further discussion of clinically relevant improvements in patients, such as the impact on fertility, body mass and bone density could help elucidate these questions.

4. COMP list of issues

- Significant Benefit

In view of the failure of the pivotal study to meet its primary endpoint, the sponsor is requested to provide further discussion in support of significant benefit. In line with the latest advice of the COMP from protocol assistance, any normalisation of cortisol in patients is expected to be translated to other measurements of disease control in order to support a clinically relevant advantage. Further discussion of functional clinical improvement in patients (such as fertility) vis-à-vis the standard of care is expected.