AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Hydrocortisone (Efmody®)
5 mg, 10 mg and 20 mg modified-release hard capsules

Reference number: 3017

Full submission

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Hydrocortisone (Efmody®) 5 mg, 10 mg and 20 mg modified-release hard capsules. Reference number: 3017. July 2022.

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Hydrocortisone (Efmody®) 5 mg,10 mg and 20 mg modified-release hard capsules

1.0 Key facts

Assessment details	Hydrocortisone modified-release (MR) (Efmody®) for the treatment of congenital adrenal hyperplasia in adolescents aged 12 years and older and in adults. The company has requested that AWMSG consider the use of Efmody® as: • a second-line treatment in adolescents with congenital adrenal hyperplasia not adequately controlled on maximum guideline doses of immediate-release hydrocortisone; • a third-line treatment in adults with congenital adrenal hyperplasia not adequately controlled on maximum guideline doses of immediate-release hydrocortisone and/or prednisolone.
Current clinical practice	Clinical practice guidelines recommend glucocorticoid replacement therapy for adults and adolescents with congenital adrenal hyperplasia. First-line treatment is immediate-release formulations of hydrocortisone in all ages that may need to be administered up to four times daily owing to the short elimination half-life of the active substance. Higher potency glucocorticoids such as prednisolone and dexamethasone that have a longer duration of action may also be used in adults with congenital adrenal hyperplasia as a second-line treatment option. However, these are not recommended in the paediatric population due to the greater growth suppressive risks. Efmody® is the first modified-release formulation of hydrocortisone licensed for treating congenital adrenal hyperplasia. It is designed to deliver hydrocortisone in a way that closely mimics the physiological circadian rhythm. Efmody® is administered in a twice daily regimen, titrated according to clinical need. Clinical expert opinion suggests that Efmody® fulfils an unmet need for patients whose disease is poorly controlled with current available treatment options.
Clinical effectiveness	The main evidence comes from an open-label, randomised, phase III study in adults comparing Efmody® with standard treatment involving other corticosteroid medicines. The primary endpoint of change in 24-hour mean standard deviation score for 17-hydroxyprogesterone at 24 weeks was not met but did show a numerical improvement. Efmody®

	improved androgen control (shown by reduced levels of 17-hydroxyprogesterone) compared with those given standard treatment. Measurements also showed that Efmody® provided better control of early morning 17-hydroxyprogesterone levels. Supportive data from an ongoing continuation study indicated that Efmody® maintained control of hormone balance longer term (at least [commercial in confidence text removed]). In some cases, using lower doses of corticosteroid than before and thus reducing the risk of side effects from long-term treatment. The clinical studies of Efmody® did not include adolescents. The Medicines and Healthcare products Regulatory Agency considered it acceptable to extrapolate efficacy and safety data from adults to adolescents. The licence was granted based on the whole of the data that showed Efmody® improved androgen control. This effect was considered clinically relevant.
Cost-effectiveness	A cost-utility analysis compares Efmody® with a basket of glucocorticoid replacement therapy in the treatment of congenital adrenal hyperplasia. The company base case suggests an incremental cost-effectiveness ratio (ICER) of [commercial in confidence figure removed] per quality-adjusted life-year (QALY) gained based on a Wales Patient Access Scheme discount. Based on sensitivity and scenario analyses provided by the company, AWTTC considers the most plausible ICER range to be between [commercial in confidence figure removed] per QALY gained. The results are primarily determined from the effects within the sub-models characterizing comorbidities associated with congenital adrenal hyperplasia. Uncertainties relating to the obesity comorbidity assumptions have a substantial effect on the ICER.
Budget impact	The company estimates that [commercial in confidence figure removed] patients are eligible to receive treatment with Efmody® in Wales in Year 1, increasing to [commercial in confidence figure removed] patients in Year 5. The company estimates that for the sub-population of patients whose disease is not adequately controlled on maximum guideline doses of standard glucocorticoid therapy, there will be [commercial in confidence figure removed] patients in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The company base case suggests additional medicine acquisition costs of [commercial in confidence

	figure removed] in Year 1 increasing to [commercial in confidence figure removed] in Year 5. The base case also predicts NHS resource savings of £26 in Year 1 increasing to £431 in Year 5 resulting from lower diagnostic and monitoring costs and lower adverse event costs.
Additional factors to consider	Efmody® does not have Medicines and Healthcare products Regulatory Agency designated orphan status. The company considers Efmody® is eligible to be considered as an orphan-equivalent medicine.

This assessment report is based on evidence submitted by Diurnal Limited and an evidence search conducted by AWTTC on 19 October 2021[1].

2.0 Background

2.1 Condition and clinical practice

Congenital adrenal hyperplasia (CAH) is a rare, inherited disorder in which the adrenal glands are unable to make an enzyme that stimulates the adrenal glands to release the glucocorticoid hormone cortisol[1,2]. In 95% of cases this enzyme is 21-hydroxylase and this leads to varying degrees of cortisol (glucocorticoid) and aldosterone (mineralocorticoid) deficiency[3]. The clinical manifestations of CAH include low blood pressure, electrolyte disturbance and a risk of adrenal crisis under conditions of physical or emotional stress[2,3]. In addition, CAH is associated with androgen precursor accumulation leading to virilisation in females, premature development of sexual characteristics in males and infertility in both sexes[2,3].

The main goal of CAH treatment is glucocorticoid therapy to replace the deficiency in cortisol hormone and minimise excess production of androgens[2]. Current standard treatment consists of immediate-release formulations of hydrocortisone that may need to be administered up to four times daily because of its short half-life[3]. This leads to fluctuations in plasma cortisol and declining levels of plasma cortisol during the night, with a corresponding rise in circulating androgen precursors[3]. Higher potency long-acting glucocorticoids such as prednisolone and dexamethasone may be used in adults with CAH as a second-line treatment option[2-4]. The Endocrine Society clinical practice guideline on congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency does not recommend dexamethasone and prednisolone in adolescents because of potent growth-suppressive effects[4].

The challenge with all standard-of-care glucocorticoid regimens in CAH is to maintain a balance between adequate control of androgen excess and the adverse effects associated with over treatment[3,5]. There is an unmet need for more physiological hydrocortisone replacement that allows for control of cortisol and androgen levels, without exposing patients to unnecessarily high steroid doses[2].

2.2 Medicine

Efmody® is a modified-release hard capsule formulation of hydrocortisone that shows delayed, followed by sustained, release of hydrocortisone[3]. Efmody® aims to provide cortisol replacement over a 24-hour period that closely mimics the normal diurnal pattern, giving a night-time rise in cortisol[3].

The European Medicines Agency granted marketing authorisation to Efmody® in May 2021 and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) granted it marketing authorisation in July 2021[2,3]. It is licensed to treat congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and in adults[2,3].

The recommended replacement doses of Efmody® in adults and adolescents who have completed growth are 15 to 25 mg/day. In adolescents aged 12 years and over who have not completed growth, the doses are based on height and weight (10 to 15 mg/m^2 daily)[6]. The daily dose can be adjusted as necessary based on the individual response. When starting treatment the total daily dose should be split into two doses with two-thirds to three-quarters of the dose given in the evening at bedtime and the rest given in the morning[6].

Patients may have to take additional immediate-release hydrocortisone during periods of mental or physical stress including surgery and infections[6].

2.3 Comparators

The comparators included in the company's submission are glucocorticoid therapies, including:

- immediate-release formulations of hydrocortisone;
- prednisolone;
- dexamethasone; and
- hydrocortisone granules (Alkindi®)[1].

2.4 Guidance and related advice

- Endocrine Society (2018) Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline[4]

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, hydrocortisone (Efmody®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

3.0 Clinical effectiveness

The company's submission includes data from two clinical studies of Efmody® in patients with CAH (DIUR-003 and the main, pivotal study DIUR-005), and an extension study (DIUR-006) which is expected to complete in February 2022[1]. Studies DIUR-005 and DIUR-006 are discussed in more detail below. Study DIUR-003 was an open-label, multiple dose, phase II study in 16 patients with CAH. It was conducted to inform on dose and study design of the subsequent phase III DIUR-005 study and will not be discussed further.

3.1 DIUR-005

Study DIUR-005 was a multicentre, open-label, randomized controlled phase III study of the efficacy and safety of Efmody® in 122 patients with CAH[2,7]. The study lasted for six months and was conducted in seven countries, including four sites in the UK[2,7].

To be included in the study, people aged 18 years and older with CAH due to 21-hydroxylase deficiency diagnosed in childhood had to have:

- documented (at any time) elevated 17-hydroxyprogesterone (17-OHP) and/or androstenedione (A4); and
- be receiving treatment with hydrocortisone, prednisolone or dexamethasone (or a combination of these glucocorticoids); and
- be stable on glucocorticoid therapy for at least six months[2,7].

Patients were excluded if they were taking medicines that interfere with glucocorticoid metabolism; if they had had a bilateral adrenalectomy; or if their work involved night shifts[2,7].

Patients were randomly assigned to receive open-label treatment for six months with either Efmody® twice daily (n = 61) or their standard glucocorticoid therapy (n = 61)[2,7]. The starting dose of Efmody® given was the hydrocortisone equivalent of their previous glucocorticoid dose with the hydrocortisone dose calculated as prednisolone dose multiplied by 5 and dexamethasone dose multiplied by 80 (up to a maximum starting dose of Efmody® 30 mg), with approximately one-third (10 mg) of the dose taken at 07:00 hours and two-thirds (20 mg) taken at 23:00 hours. Dose titrations for both treatment groups were made at 4 and 12 weeks using identical rules, following advice by two independent physicians blinded to all data except 24-hour hormone profiles and an investigator-completed adrenal insufficiency checklist[7]. In the event of intercurrent illness or other reasons that required additional glucocorticoids, the 'sick day rules' were followed[2,7].

The median daily dose of hydrocortisone was 25 mg at baseline; at six months it was 31 mg in the group on standard glucocorticoid therapy and 30 mg in the group taking Efmody®[7]. At six months, patients could then either return to their standard glucocorticoid therapy or enter the extension study, DIUR-006 to continue to receive Efmody®[7].

The main measure of effectiveness was a score based on levels of 17-OHP, a fall in this score showed better disease control[3,7]. Blood levels of the adrenal androgen precursors 17-OHP and A4 (used for monitoring androgen levels) were measured at baseline, 4, 12 and 24 weeks every two hours from 15:00 to 15:00 hours[7].

The study did not meet its primary endpoint of a statistically significant change in 24-hour mean standard deviation score (SDS) for 17-OHP at 24 weeks: a difference in least squares (LS) means of −0.07 (95% confidence interval [CI] −0.30 to 0.16; p = 0.55)[2]. Although Efmody® did show a numerical improvement in biochemical control, over the 24 weeks of the study the 17-OHP score fell by 0.40 in patients treated with Efmody® compared with 0.17 in those given standard treatment[2].

To examine the potential wider benefits of Efmody® which were not captured by the primary and secondary study endpoints the applicant company performed a range of post-hoc analyses[2]. To explore the morning improvement in biochemical control the primary efficacy analysis was repeated using 8-hour profiles instead of 24-hour profiles. The difference between the two treatment groups in the 07:00 to 15:00 hour profile was statistically significant: a difference in LS means of −0.29 (95%CI −0.56 to −0.01; p = 0.044). The other 8-hour profiles did not show a difference[2].

The post-hoc analysis also considered the reduction in 17-OHP area under the curve (AUC) throughout the duration of the study. The change in 17-OHP values from baseline to Week 24 showed a greater reduction in range in the Efmody® treatment group (a difference in LS means of −13.77 [95% CI −25.78 to −1.76; p = 0.025]), consistent with less variable and more controlled 17-OHP concentrations[2].

A responder analysis (decline of 17-OHP to the target levels aimed for in clinical practice) at 09:00 hours showed an increase in responders in the Efmody® treatment group, from [commercial in confidence figure removed] at baseline to [commercial in confidence figure removed] at Week 24[2]. In the group who received their usual glucocorticoid therapy the proportion of responders was [commercial in confidence figure removed] at baseline and 30% at Week 24. At Week 24, 90.6% of patients in the Efmody® group had a 09:00 hours 17-OHP level below 36 mmol/litre, compared with 71.2% of patients in the usual glucocorticoid therapy group[1,2].

No significant differences were demonstrated between the Efmody® group and the usual glucocorticoid treatment group for the secondary endpoints of A4 levels or body mass and bone mineral density (measured by DEXA scan)[2]. No significant differences in patients' quality of life were observed between the two treatment groups[2].

Glucocorticoid stress dosing was reported by 26 patients in the Efmody® treatment group and 36 patients in the group receiving standard glucocorticoid treatment[7]. Fewer patients in the Efmody® treatment group had sick day episodes where increased glucocorticoid stress dosing was required (26 [42.6%] in the Efmody® group compared to 36 [59.0%] in the glucocorticoid treatment group)[6].

No patients experienced adrenal crises in the Efmody® treatment group compared to three patients in the standard glucocorticoid treatment group[7].

Additional post-hoc analyses were carried out in 39 patients who had previous treatment with prednisolone (+/- supplementary hydrocortisone). Of these 39 patients, 22 had disease control (9 am 17-OHP < 36 nmol/L) at baseline. At 24 weeks, 17 patients (94%) in the Efmody® treatment group and 15 patients (71%) in the standard glucocorticoid treatment group showed disease control.

3.2 Study DIUR-006

DIUR-006 is an ongoing, phase III, open-label, long-term (up to 3.7 years) extension study that enrolled patients who completed study DIUR-005 and study DIUR-003[1,2]. Patients continued with Efmody® treatment or switched from their current glucocorticoid therapy to Efmody®. A total of 91 patients were enrolled into the study. Assessments were conducted at weeks 4, 12 and 24 after starting study DIUR-006, and at six-monthly intervals. The study's primary endpoint is the safety of Efmody® over time[1,2].

During the extension study, doses of Efmody® were reduced[1]. The total daily dose fell from a median of 30 mg at baseline to a median of 20 mg at Month 12, [commercial in confidence figure removed][1].

At the time of data cut-off (30 April 2020), 74 patients remained on treatment in the study[1]. Data from the third interim analysis (from August 2016 to April 2020; 44 months) showed that patients achieved a similar or better disease control defined by

17-OHP values at 09:00 hours and at 13:00 hours when compared with the percentage of patients achieving disease control at baseline[1]. In study DIUR-006, the mean frequency of adrenal crisis was reported to be [commercial in confidence figure removed] adrenal crises per 100 patient years[8].

3.3 Safety information

Pooled data from clinical studies DIUR-003, DIUR-005 and DIUR-006 show most patients experienced mild or moderate treatment-emergent adverse events (TEAEs) across both treatment groups[2]. The most frequently reported TEAEs for Efmody® use include fatigue (11.7%), headache (7.5%), and increased appetite (5.8%)[2]. These adverse events are to be expected in patients treated with corticosteroids; however, they were more common in the Efmody® group than in the group taking standard glucocorticoid therapy[2].

Serious adverse events (SAEs) reported in 19 patients taking Efmody® were: acute adrenocortical insufficiency (2.5%), gastroenteritis (3.3%) and diverticulitis (1.7%). All SAEs resolved and there were no deaths in any of the clinical studies of Efmody®[2]. In addition, pooled data did not indicate any increased risk for adrenal crisis with Efmody® compared to standard glucocorticoid therapy[2].

In study DIUR-005, the signs and symptoms of adrenal insufficiency or over-treatment were higher in patients who received Efmody® (35 patients; 57.4%) than in those who received standard glucocorticoid treatment (26 patients; 42.6%)[2]. These adverse events were mainly reported during the first 12 weeks of the study, during the titration phase[2].

Pooled analysis showed a total of 26 patients (21.7%) treated with Efmody® had an unexpected therapeutic response, as did one patient (1.6%) treated with standard glucocorticoid therapy[2]. In study DIUR-005 the majority of these events can be summarised as improvement of mood, alertness and energy and improvement in reproductive hormone regulation[2]. The Committee for Medicinal Products for Human Use (CHMP) noted the observed beneficial effect cannot be attributed to the Efmody® treatment as a less optimal pre-baseline treatment regimen cannot be excluded[2].

No adolescents aged 12 to 17 years were included in the clinical studies of Efmody®[2,6]. Hydrocortisone has been used for more than 60 years in paediatric CAH patients with a safety profile similar to that in adults[2,6]. The CHMP considered it acceptable to extrapolate safety data from adults to adolescents[2]. The Summary of Product Characteristics (SmPC) outlines precautions in line with the known safety profile of oral hydrocortisone, including warnings on growth retardation in adolescents and the requirement of additional monitoring[6].

The CHMP concluded that the safety of Efmody® is comparable to the well-known safety profile of oral hydrocortisone[2].

3.4 Ongoing studies

Study DIUR-006 is expected to finish in the first half of 2022 and will provide additional evidence by the end of 2022[1].

3.5 AWTTC critique

- Efmody® is the first licensed modified-release formulation of hydrocortisone for treating CAH. Efmody® is designed to deliver hydrocortisone in a way that closely mimics the physiological circadian rhythm, which cannot be achieved with immediate-release or long-acting glucocorticoids[2].
- The applicant company requests that Efmody® is considered for use for people with CAH whose condition is not adequately controlled on maximum guideline doses of immediate-release hydrocortisone and/or prednisolone.
- The company has highlighted a post-hoc analysis that considers androgen control in patients who have previously received prednisolone (+/- supplementary hydrocortisone); 22 (56%) patients were on prednisolone doses above the maximum recommended guideline doses and 17 (44%) patients had uncontrolled androgen levels at baseline. It is unclear what proportion of patients are sub-optimally controlled after treatment with immediate-release hydrocortisone at baseline.
- Clinicians in Wales indicate Efmody® fulfils an unmet need for patients who have suboptimal biochemical levels of 17-OHP despite adequate standard glucocorticoid dosing or where immediate-release hydrocortisone is associated with compliance issues. Clinical experts estimate that in Wales around 40% of patients with CAH are poorly controlled on standard glucocorticoid treatment and would therefore be eligible for Efmody®.
- AWTTC-sought clinical experts confirmed the company's submission comparators are appropriate although highlighted that dexamethasone is used very rarely in clinical practice as it tends to drive significant weight gain.
- Study DIUR-005 failed to meet its primary endpoint and did not show superiority over standard glucocorticoid therapy[2]. The CHMP noted that although using standard deviation score to depict hormone levels is accepted as common practice, it might have contributed to the study's failing to show clinical superiority along with the aggressive titration regimen used in the study[2]. The titration issue has been addressed through appropriate dosing recommendations in the SmPC[2,6].
- Additional post-hoc analyses supported the efficacy of Efmody® in people with CAH. The analysis considered most clinically relevant was the early morning profile (07:00 to 15:00) that demonstrated a statistically significant reduction in 17-OHP. Responder analysis also demonstrated a greater proportion of patients in the Efmody® treatment group with reduced morning (9.00 hrs) levels of 17-OHP. The licence was granted based on the whole of the data that showed Efmody® improved androgen control compared to standard glucocorticoid therapy[2].
- The reduction in early morning 17-OHP peaks may reduce the effect of excess androgens on sexual development and prevent problems associated with infertility[2,3]. Welsh clinical experts highlighted these are important patient-related clinical benefits associated with Efmody® treatment.
- Clinical studies of Efmody® did not include adolescents aged 12–17 years[2]. The CHMP considered it acceptable to extrapolate efficacy and safety data from adults to adolescents on the basis of the recommendation for dose titration according to clinical need, as well as dosing based on body surface area in growing adolescents[2,3].
- In the long-term extension study (DIUR-006) further dose reductions were possible while maintaining androgen control, reducing the risk of adverse effects associated with long-term glucocorticoid therapy[2].

- The clinical characteristics of Efmody® treatment, such as a delayed-release effect replicating the circadian rhythm and glucocorticoid-sparing effect, may provide added clinical value for patients[2]. The twice-daily regimen may also help with treatment adherence compared with immediate-release hydrocortisone[2].
- In study DIUR-005, there were no differences between the treatment groups for clinically relevant secondary endpoints such as total body mass, fat and lean mass, bone mineral density and quality of life outcomes[2]. However, the CHMP noted that the study lasted only six months, and any effect on clinical endpoints might take longer to occur[2].
- In study DIUR-005, the frequency of adverse events was higher in patients switching from their standard glucocorticoid treatment to Efmody® treatment[2]. The difference could be partly due to the aggressive titration regimen of Efmody® used in the study and the open-label design of the study, in which patients who remained on their current glucocorticoid treatment might be less likely to report adverse events[2,3].
- In study DIUR-005, the two treatment groups had different levels of disease control at baseline[7]. At the end of the study, 28 of 33 (85%) of those not under control at baseline were controlled in the Efmody® group, compared to 10 of 20 (50%) in the standard treatment group[7].
- The applicant company suggests Efmody® may protect growth and pubertal development in adolescents[1]. However, there are no clinical outcome data in adolescents to support this.

4.0 Cost-effectiveness

4.1 Context

The company's submission includes a cost-utility analysis comparing Efmody® with a basket of glucocorticoid replacement therapies in patients with congenital adrenal hyperplasia (CAH). The company reports that the model reflects the sub-population for use for patients whose condition is not adequately controlled on maximum guideline doses of immediate-release hydrocortisone and/or prednisolone. This is because the expected utility gain from Efmody® is the same regardless of the comparator arm because all the standard glucocorticoids are expected to have the same utility decrements.

The cost-utility analysis takes the form of a de novo Markov model structured as a core model that reflects the direct effect of CAH which is further supplemented by a series of sub-models to investigate the impact of Efmody® in CAH. The model considers a lifetime horizon comprising monthly cycles and adopts an NHS Wales and Personal and Social Services perspective. Costs and outcomes are discounted at 3.5%. The submission incorporates a complex Wales Patient Access Scheme (WPAS) based on a simple percentage discount.

Patients enter the model at the age of 12 years with a diagnosis of CAH and either remain in an alive CAH state or transition to death. The alive CAH states reflect the core model health states of routine care or adrenal crisis, or one of the six co-morbidity sub-models, namely: obesity, fertility, diabetes, bone health, cardiovascular disease (CVD) and height (adolescents only). The core model considers the direct impact that Efmody® has on costs and QALYs associated with CAH. This includes treatment acquisition and monitoring costs, as well as outcomes

associated with sick day rules resulting from periods of illness or stress that require increased doses of medication to meet the natural increased demand for cortisol. The sub-models consider the impact of Efmody® on the six associated co-morbidities. The use of Efmody® in patients with CAH provides physiological cortisol replacement resulting in improved normalized cortisol and androgen levels compared to patients being treated with standard glucocorticoid replacement therapy, and therefore Efmody®-treated patients subsequently experiencing a reduced effect from comorbidities.

Incidence of each comorbidity is informed by a combination of observed data from the pivotal clinical studies DIUR-005[9] and DIUR-006[8], and published literature. Incidence of adrenal crisis is sourced from DIUR-006[8] for the Efmody® arm, and from the literature for the comparator arm. Incidence rates for all other comorbidities were sourced from the literature. For CVD, obesity, diabetes and fractures, the rate of comorbidities was defined by the CAH impact and the impact of glucocorticoid treatment. These effects were applied multiplicatively to determine the proportion of patients incurring comorbidities in each cycle.

The efficacy data used to inform the transition probabilities are derived from extrapolating data from a range of sources including the DIUR-005[9] and DIUR-006[8] clinical trials and published literature. The DIUR-006 study also demonstrated a clinically meaningful steroid sparing effect with Efmody® [8]. After 12 months, a proportion of patients are modelled to receive a dose reduction to 20 mg per day as opposed to 25 mg to reflect improved disease control.

The company also suggests the use of Efmody® will lead to greater adherence due to a simplified dosing regimen and allow for consistency as patients transition from adolescent to adult care. Additional assumptions from clinical opinion include a 15% reduction in resource use, and a reduction from three to two sick day periods per year for patients receiving Efmody®.

Patients with CAH are expected to have lower utility than the general population which is captured in the model through a detrimental effect on utility in each of the comorbidity sub-models. The core model does not include any utility decrement associated with CAH as validated by clinical opinion[10]; instead utility is defined by general population values[11]. Utility decrements are combined multiplicatively to reflect the total impact on health-related quality of life associated with each treatment. Similarly, for mortality a multiplier for each comorbidity is identified and combined multiplicatively, and then applied to age-related general population mortality values[12].

The costs for the core model consist of medicine acquisition costs, concomitant medication costs and monitoring costs inflated to 2019 prices where applicable. Resource use for Efmody® is based on dosing from DIUR-006[8] whilst comparator dosing is based on a basket of therapies (prednisolone, dexamethasone, and Alkindi®) according to clinical guidelines[4] and clinical opinion[10]. Usage of concomitant medications and additional medication costs associated with sick-day rules were informed by the DIUR-005 study[9] and clinical opinion[10]. Medication unit costs are sourced from the Drugs and Pharmaceutical Electronic Market Information Tool (eMIT)[13]. Monitoring costs consider the tests and appointments that patients with CAH require, with estimates of frequency informed by clinical opinion[10] and unit costs sourced from conventional published sources[14,15]. The costs of each comorbidity were derived from clinical opinion and the literature, using clinical guidelines and

NHS reference costs[15]. There were no costs associated with managing obesity or height.

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the base case model results. The parameters tested include altering the proportion of male:female patients, number of sick day occurrences per year, incidence and mortality of cardiovascular events across age groups, changes to individual resource use frequency and costs, and utility decrements associated with comorbidities. Scenario analyses also explore changes to the discount rate, exclusion of individual sub-models, and dosage changes in both hydrocortisone and glucocorticoid replacement therapy.

4.2 Results

The results of the base case analysis are detailed in Table 1. When compared with standard glucocorticoid therapy, Efmody® is [commercial in confidence figure removed] more costly and produces an additional 3.25 quality-adjusted life-years (QALYs) over the lifetime time horizon. The higher costs are predominantly driven by higher treatment acquisition costs of Efmody®. Costs associated with monitoring and comorbidities are higher for the standard glucocorticoid therapy arm. The incremental cost-effectiveness ratio (ICER) for Efmody® compared to standard glucocorticoid therapy generated is [commercial in confidence figure removed] per QALY gained when the WPAS is taken into account. The higher number of QALYs for Efmody® is a result of higher mortality multipliers and lower utility multipliers associated with comorbidities in the standard glucocorticoid therapy arm.

Table 1. Results of the base case analysis

	Efmody®	Standard glucocorticoid therapy	Difference
Medicine acquisition costs	¶¶	£11,408	¶¶
Monitoring costs	£2,918	£3,884	−£966
Concomitant medication costs	£6,246	£5,758	£488
Total comorbidity costs	£13,854	£28,195	−£14,341
Total costs	¶¶	**£49,244**	¶¶
Total life-years	58.41	50.57	**7.83**
Total QALYs	19.02	15.77	**3.25**
ICER (£/QALY gained)	¶¶		

¶¶: commercial in confidence figure removed
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

The results for the univariate sensitivity analyses show that the ICER is most sensitive to the relative risk of obesity in the standard glucocorticoid therapy arm, the relative risk of obesity in the hydrocortisone arm, followed by CAH and glucocorticoid dose impact on growth. In each of these cases, the ICER remains broadly within the usual acceptable threshold between <£20,000 and <£30,000 per QALY gained. In the sensitivity analyses the ICER ranges between [commercial in confidence figures removed].

Probabilistic sensitivity analyses (PSA) indicate that with the WPAS applied, Efmody® has [commercial in confidence figure removed] probability of being cost-effective at a threshold of £20,000 per QALY gained increasing to [commercial in confidence figure removed] probability of being cost-effective at a threshold of £30,000 per QALY gained. The distribution of iterations indicated that there was greater uncertainty regarding the expected health benefits than the expected costs, which the company attributes to 90% of the costs being composed of medicine acquisition costs which are not varied by the PSA.

Extensive scenario analyses were conducted. Most scenarios have limited impact on the ICER. The full range of plausible ICERs ranged from [commercial in confidence figures removed]. Some scenarios considering treatment initiation, doses and assumptions relating to sub-models were considered to be most plausible. When the effects of comorbidities are excluded from the model by "switching-off" all the sub-models, costs and QALYs are defined exclusively by the core model. In this scenario Efmody® is dominated by standard glucocorticoid therapy. However, given the impact of CAH on comorbidities it is not plausible that the effects of these are removed.

The results of key scenario analyses are assessed in order of plausibility in Table 2.

Table 2. Results of scenario and sensitivity analyses

Scenario	Base case	ICER	Plausibility
Adolescent dose – 10 mg per day	Adolescents receive 15 mg of Efmody® per day	¶¶	This scenario has some plausibility with the base case. A 15 mg adolescent dose is based on clinical opinion received by the company. Adolescents with CAH have a lower body surface area compared to adults with an analysis of a range of doses showing the recreation of effect for 10 mg –15 mg of Efmody® in patients that are still growing[10].
BMI reduction is over 24 months	Any reduction in BMI as a result of Efmody® would occur over 12 months.	¶¶	These scenarios have some plausibility over the base case as the DIUR-006 study shows a steady reduction in total fat mass in the Efmody® arm up to 36 weeks.
BMI reduction is over 36 months		¶¶	
Obesity - Utility from Sach et al.	Obesity - Utility from Kearns et al.	¶¶	These scenarios have some plausibility as they provide alternative model of

Scenario	Base case	ICER	Plausibility
Obesity - Utility from Macran et al.		¶¶	calculating disutility. The disutility in Sach et al. is related to obesity based on six BMI categories rather than a given utility value for each BMI value. In Macran et al. disutility is related to obesity based on a utility decrement for each BMI unit over a threshold of a BMI value of 21 rather than a given utility value for each BMI value.
Obesity - Only standard glucocorticoid therapy BMI increase associated with females, reflective of CaHASE	The BMI of male and female CAH patients is 1.23 greater than the general population, as reported in CaHASE	¶¶	This scenario has some plausibility as it uses the evidence from the CaHASE study by gender as opposed to applying a general obesity multiplier across both genders.
Hydrocortisone dose – 25 mg	Hydrocortisone dose of 30 mg per day	¶¶	This scenario is equally plausible as the base case scenario with the dose recommendation for adult CAH patients of 15–25 mg per day[4] by clinical interviews conducted by the company indicate higher doses of 30 mg per day are typically used in adult CAH patients. The use of 40 mg is less plausible than the base case being higher than the typical usage per day.
Hydrocortisone dose – 40 mg		¶¶	
Obesity – standard glucocorticoid therapy BMI informed by Nguyen et al.[16] (1.09) for males and CaHASE[17] for females (1.23)	The BMI of male and female CAH patients is 1.23 greater than the general population, as reported in CaHASE	¶¶	This scenario is less plausible than the base case as the BMI input for males and females is either sourced from different studies with different populations or does not differentiate across treatments.

Scenario	Base case	ICER	Plausibility
Obesity – standard glucocorticoid therapy BMI informed by Nguyen et al. (1.09) for both males and females		¶¶	
Obesity - Efmody® BMI informed by Nguyen et al. (1.09) for both males and females		¶¶	
Exclusion of individual sub-models (adrenal crisis, CVD, fractures, height, obesity, fertility, diabetes)	All sub-models included	¶¶	These scenarios lack plausibility compared to the base case as it has been shown by a variety of studies how comorbidities impact patients with CAH. The exclusion of obesity has the largest impact on the ICER whereas the exclusion of CVD has the smallest impact.
Treatment initiation at 18 years old	Treatment initiation at 12 years old	¶¶	This scenario lacks plausibility. Although the evidence from the DIUR-005 and DIUR-006 trials is based on a population of adults ≥ 18 years, the licensed indication is for both adults and adolescents ≥ 12 years. Welsh clinical experts confirm Efmody® would be used in this patient population.
No reduction in resource use due to hydrocortisone	15% reduction in resource use due to hydrocortisone	¶¶	This scenario lacks some plausibility as increased patient adherence reduces the burden of disease

Scenario	Base case	ICER	Plausibility
			monitoring and reduces healthcare resource use.
1.5% discount rates for cost and health outcomes	3.5% discount rates for cost and health outcomes	¶¶	This scenario lacks plausibility as it does not sufficiently discount future costs and effects. The base case discount rate is consistent with the NICE reference case[18]. The results for this scenario show that the ICER is relatively insensitive to changes in the discount rate.

¶¶: commercial in confidence figure removed

BMI: body mass index; CAH: congenital adrenal hyperplasia; CaHASE: United Kingdom Congenital Adrenal Hyperplasia Adult Study Executive; CVD: cardiovascular disease; ICER: incremental cost-effectiveness ratio; NICE: National Institute for Health and Care Excellence

4.3 AWTTC critique

The submission is characterized by strengths and limitations.

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model.
- The model reflects the relevant patient population. Because CAH is a chronic lifelong disease, the adoption of a lifetime horizon is considered appropriate.
- The company has made an effort to use the best available data. Model inputs related to comorbidities were sourced from a range of published evidence, validated by clinical experts, and every comorbidity was assumed to have a detrimental impact on quality of life.
- Extensive sensitivity and scenario analyses were conducted. Numerous methods have been used to try to validate the model including: extreme value analysis and clinical expert validation in relation to the clinical plausibility.

Limitations:

- The model appears to be heavily influenced by the impact that Efmody® has on the comorbidities of CAH which are a key driver of the ICER. The impact of removing each sub-model and comorbidity has been tested in the scenario analyses. When all the sub-models are simultaneously deactivated, with results defined solely by the core model, Efmody® is dominated by standard glucocorticoid therapy with the difference in costs defined exclusively by

higher drug acquisition costs for Efmody®. However, excluding the effects of Efmody® on all comorbidities is not considered clinically plausible since it is expected that Efmody® will demonstrate improved patient symptomology.

- The patient population for the DIUR-005[9] and DIUR-006[8] studies comprised adults aged ≥ 18 years with CAH whereas the model and licensed indication includes adolescents with CAH (aged ≥ 12 years). Whilst the EMA has approved the validity of extrapolating adult data to an adolescent population and adolescent dosing criteria are supported by a physiologically-based pharmacokinetic (PBPK) model, any difference in efficacy could impact the presented cost-effectiveness estimates for Efmody®. Scenario analysis presented by the company for a population excluding adolescents < 18 years produced a 3.5% increase in the ICER.
- The primary endpoint of the DIUR-005[9] study was not reached. Whilst the treatment effect was observed in both the treatment and comparative arms the between group difference, whilst favoring the intervention, was not statistically significant. Post-hoc analysis of the primary endpoint indicated evidence of improved control of 17-OHP and further evidence of the benefit of Efmody® over glucocorticoid therapy. Improved control of androgens was observed for both the treatment and comparator glucocorticoid therapy group, driven by approved adherence to the titration regimen. It is unclear whether such an improvement in either arm would be seen outside the controlled study environment. However, the dose titration in DIUR-006 more closely reflected the real world with similar benefits of Efmody® observed.
- In the core-model, there is no utility decrement associated with CAH with utility equal to general population utility. Utility decrements are associated only with comorbidities. It is unclear whether CAH contributes to an additional utility decrement.
- No adrenal crisis was reported in the DIUR-005[9] comparative trial, therefore incidence of adrenal crisis is sourced from DIUR-006[8] for the Efmody® arm with a higher incidence sourced from the literature for the comparator arm. The comparative study had a large sample size with a closely aligned definition of adrenal crisis to the definition in DIUR-006[8,19], but the use of different sources may induce bias to the modelled estimate.
- The model inputs are heavily influenced by the role of clinical opinion which informs the dosing of the basket of comparator therapies, estimates on the frequency of resource use, and sick day rules. Clinical opinion has also been sought on various assumptions within the model including the length of sick day periods and the assumption that patients receiving Efmody® results in a 15% reduction in resource use. As CAH is a rare disease there are limited published data on patient outcomes; therefore, clinical opinion was necessary to populate model inputs. The impact of these assumptions on the results was tested by extensive scenario analysis which typically did not show a large impact on the ICER. For example, the assumption of no resource use reduction associated with Efmody® increases the base-case ICER from [commercial in confidence figures removed] per QALY gained.
- No costs are associated with either the height or obesity sub-models. Should the costs not be incorporated into other comorbidities in an attempt to avoid double counting, their omission may result in an underestimate of total costs.
- Adverse events related to the medication are incorporated into the model using sick day rules. Data from the DIUR-005[9] study indicate that patients in the standard glucocorticoid therapy arm have a higher number of sick days than those on Efmody®. In the model, the sick day rules result in greater costs

but do not appear to have an impact on utility due to their short duration (3 days) and infrequent occurrence (2–3 times per year). A small number of patients with adverse events discontinue on the study treatment (n = 1) which does not appear to be incorporated into the model. Inclusion of discontinuation would likely have a negligible impact on the cost-effectiveness results.

4.4 Review of published evidence on cost-effectiveness

A review conducted by All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any studies relevant to the cost-effectiveness of Efmody® versus standard glucocorticoid therapy in the treatment of patients with congenital adrenal hyperplasia.

5.0 Summary of evidence on budget impact

5.1 Context and methods

The company has estimated that there will be 177 people with CAH in Wales in 2021. This estimate is based on population projections by year and age by Stats Wales[20] and an incidence rate of 1/18,000[21]. This incidence is assumed to be constant over the five-year time horizon taking into account population growth but not mortality. Of these patients, 86.86% are assumed eligible for treatment in Year 1 increasing to 91.48% in Year 5 based on the number of CAH patients in Wales over 12 years of age. The sub-population of eligible patients is assumed to be 40% based on feedback from Welsh endocrinology. Discontinuation is not taken into account and an uptake rate of 4% is assumed in Year 1 increasing to 60% in Year 5. This results in an estimated 2 patients receiving Efmody® in Year 1 increasing to 40 patients in Year 5. The acquisition cost per patient was estimated at [commercial in confidence figure removed] per patient in Year 1 reducing to [commercial in confidence figure removed] in Year 5. The reduction in cost over time is due to patients transitioning from a higher treatment initiation dose in Year 1 to a lower final treatment dose in subsequent years, with [commercial in confidence figure removed] of patients on subsequent treatment or final treatment doses in Year 5.

The company performed basic sensitivity analysis altering the uptake rates and medicine acquisition costs by 10%.

5.1 Results

The budget impact is presented in Table 3. The company estimates that introducing Efmody® would lead to an overall cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of currently available standard glucocorticoid therapy. Sensitivity analysis changing uptake rates and medicine acquisition costs by 10% resulted in cost differences between [commercial in confidence figure removed] in Year 1 and [commercial in confidence figure removed] in Year 5.

Table 3. Company-reported costs associated with use of Efmody® for the treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults

	2021	2022	2023	2024	2025
Number of eligible patients (all licensed indications)	153	157	161	164	168
Sub-population of eligible patients (indication under consideration)	61	62	64	66	67
Uptake of new medicine (%)	4%	10%	30%	40%	60%
Number of patients receiving new medicine allowing for discontinuations	2	6	19	26	40
Medicine acquisition costs in a market without new medicine	£4,963	£5,045	£5,106	£5,261	£5,291
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£651	£1,653	£5,119	£7,039	£10,719
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶: commercial in confidence figure removed

The company estimates that net resource implications arising from the introduction of Efmody® will lead to a saving of £26 in Year 1 increasing to £431 in Year 5. This is primarily a consequence of reduced diagnostic and monitoring costs due to greater adherence with Efmody®. These resource type savings are included for potential planning purposes but may not be realized in practice.

5.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact. The company has factored population growth into the calculations but has not factored in mortality or discontinuation; therefore, the budget impact is considered conservative.
- The budget impact considerations include acquisition costs and other resource use costs such as supportive medicines costs (i.e. concomitant medication and sick day medication) but do not take into account costs associated with CAH related comorbidities. The budget impact is therefore likely a conservative estimate.

6.0 Additional factors to consider

6.1 Medicines developed to treat rare diseases

Consideration is required as to whether Efmody® should be considered as an orphan equivalent medicine.

While the medicine does not have European Medicines Agency (EMA) designated orphan status, the applicant company suggests Efmody® should be considered as an orphan-equivalent medicine. Welsh clinical expert opinion indicates the full population of the licensed indication does not exceed the threshold of ≤ 5 patients in 10,000 (≤ 1,500 patients in Wales).

New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 4) if they consider Efmody® is a medicine developed to treat a rare disease.

Table 4. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
Severity of the disease	Congenital adrenal hyperplasia (CAH) is a rare genetic disorder that affects the adrenal glands. There is no cure for CAH, yet with proper treatment, most people can live normal lives. The condition is characterised by adrenal insufficiency and androgen excess. Androgen excess leads to virilisation in females, premature development of sexual characteristics in males and infertility in both sexes.
Unmet need	The company suggests existing treatments in CAH are inadequate given that they fail to mirror physiological cortisol levels, do not control excess androgen levels and expose patients to overtreatment with steroids. The company claims there is a need for new treatment approaches that can closely mimic the circadian cortisol profile and subsequently achieve optimal disease control of CAH.
Innovative nature of the medicine	The applicant company claims that Efmody® is able to replicate the physiological profile of cortisol over a 24-hour period and provide superior androgen control with a clinically relevant daily steroid dose reduction compared with standard glucocorticoid treatment. Furthermore, as Efmody® has a simpler dosing regimen, the company suggests this should contribute to better treatment adherence and disease control.
Societal impact on non-health benefits that may not adequately be captured in the QALY	A wider societal analysis of Efmody® has not been conducted by the company. The company contends that the inclusion of a societal perspective would likely enhance the cost-effectiveness of Efmody® under the assumption that the new medicine regimen will lead to greater disease control and a positive impact on caregivers' and families' lives.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; CAH: congenital adrenal hyperplasia; NMG: New Medicines Group	

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