New Medicine Assessment

Hydrocortisone Modified-Release Capsules (Efmody®)

For Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over, and adults

Recommendation:

AMBER 0 for the 2nd line treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over, and adults, in the following circumstances:

1. **Patients showing signs of excess steroid replacement with alternative preparations such as prednisolone and hydrocortisone**
2. **Patients who have a specific difficulty with taking multiple daily doses of hydrocortisone**
3. **Patients developing Testicular Adrenal Rest Tumour (TART).**
4. **Patients desiring and not achieving fertility**
5. **Problems with pubertal growth and development (paediatrics)**

The dose of hydrocortisone and the patient's clinical condition should have been stabilised and reviewed prior to prescribing responsibility passing to primary care clinicians.

Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

When recommending or handing over care, specialists should ask primary care prescribers to take over prescribing responsibility, and should give enough information about the indication, dose, monitoring requirements, use outside product licence and any necessary dose adjustments to allow them to confidently prescribe.

Summary of supporting evidence:

- The EMA concluded that overall, the clinical characteristics of Efmody® treatment (delayed release effect mimicking physiological circadian rhythm, twice daily dosing, glucocorticoid sparing effect) were considered of added clinical value for patients. [1]
- The reported adverse events of Efmody® are considered to be in line with those known for oral hydrocortisone. [1]
- In the 24 hour 17-OHP curve early morning peak, a greater reduction was observed in the hydrocortisone modified-release group compared with standard glucocorticoid therapy. [2]
- A glucocorticoid sparing effect was seen in the overall population. In the long-term extension study, further dose reductions of Efmody® were possible without losing androgen control, suggesting a more optimal dosing. This finding is considered of additional clinical benefit for the patients, given the adverse consequences of long-term glucocorticoid treatment. [2]

Date: February 2023

- The Scottish Medicines Consortium do not recommend the use of Efmody® within NHS Scotland for the treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults because “The submitting company did not present sufficiently robust clinical and economic analysis to gain acceptance by SMC”.

Details of Review

Name of medicine (generic & brand name)**:** Hydrocortisone Modified-Release Capsules (Efmody®)

Strength(s) and form(s): 5 mg, 10 mg, and 20 mg

Dose and administration: Recommended replacement doses of hydrocortisone are 10-15 mg/m^2 /day in adolescents aged 12 years and over who have not completed growth, and 15-25 mg/day in adolescents who have completed growth and adult patients with CAH. In patients with some remaining endogenous cortisol production a lower dose may be sufficient.

At initiation 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. Patients should then be titrated based on their individual response.

The morning dose should be taken on an empty stomach at least 1 hour before a meal and the evening dose taken at bedtime at least 2 hours after the last meal of the day. [3]

BNF therapeutic class / mode of action: Glucocorticoids

Licensed indication(s): Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over, and adults

Proposed use (if different from, or in addition to, licensed indication above): In their application East Lancashire Teaching Hospital suggested the following:

Immediate-release hydrocortisone will remain the first line treatment and will continue to be used in the majority of patients. Efmody® will be used as the second line treatment in patients with the following specific indications:

- *patients in whom acceptable biochemical control (morning 17 OH progesterone within target) cannot be achieved with 3 times daily immediate release hydrocortisone*
- *Patients showing signs of excess steroid replacement with alternative preparations such as prednisolone and hydrocortisone*
- *Patients who have a specific difficulty with taking multiple daily doses of hydrocortisone*
- *Patients developing Testicular Adrenal Rest Tumour (TART).*
- *Patients desiring and not achieving fertility*
- *Problems with pubertal growth and development (paediatrics)*

Course and cost:

For 50 pack sizes of **Efmody®**

5 mg - £135

10 mg – £270

Assuming a dose as follows:

- Adolescents aged 12 years and over who have not completed growth: 10mg to 15mg/m^2/day orally.

- Adolescents who have completed growth and adult patients: 15mg to 25mg/day orally. The resulting annual cost of these doses would be **£2,948** to **£4,914** (figures taken from the Scottish Medicines Consortium (SMC) report). [2]

NB Costs from MIMS online on 15/08/22. Adolescent cost is based on assumptions for a 14-year-old child, weighing 50kg, with a body surface area of 1.5m^2. Costs do not take any patient access schemes into consideration.

Current standard of care/comparator therapies:

30 x Hydrocortisone 10 mg tablets = £2.41

Cost taken from the August 2022 Drug Tariff.

Assuming the same dosing as above and c*osts for hydrocortisone 10 mg tablets are based on using one tablet for each dose and assume wastage of the remainder of the tablet.*

2 to 3 tablets for 365 days = **£59** to **£88**

Relevant NICE guidance:

N/A

Background and context

Adrenal insufficiency is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids. Due to the central role of these hormones in salt, and fluid homeostasis, adrenal insufficiency is a severe and potentially life-threatening condition. Primary adrenal insufficiency is rare with an estimated prevalence of 100 to 140 cases per million and an annual incidence of 4 per million. [4] The majority of cases of adrenal insufficiency in children are due to congenital adrenal hyperplasia, including 21-hydroxylase deficiency, and the incidence is estimated to range from 1 in 10,000 to 1 in 20,000 births. [5] In congenital adrenal hyperplasia, the pituitary gland compensates for the reduced cortisol formation by increasing the production of corticotrophin which in turn results in excessive adrenal androgen production. Immediate-release hydrocortisone is the standard of care in adrenal insufficiency and treatment prevents adrenal crisis and virilisation, allowing normal growth and development.

Hydrocortisone is the replacement therapy of choice in children, adolescents, and adults (according to the Endocrine Society Clinical Practice Guideline (2018) because it has lower potency and is shorter acting than prednisolone and dexamethasone and may have fewer adverse events. Oral hydrocortisone is currently available as immediate-release and modified-release tablets. Efmody® is claimed to present an 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 (without the necessary spikes in stress situations). [1] Efmody® modified-release capsules were prioritised for review by LSCMMG following a request from East Lancashire Hospitals Trust.

Summary of evidence

Summary of efficacy data in proposed use:

DIUR-005 RCT

Evidence to support the efficacy and safety of hydrocortisone modified-release for this indication is from DIUR-005, a multicentre, randomised, open-label, parallel group, phase III study. DIUR-005 recruited adult patients with classic CAH diagnosed in childhood with

documented (at any time) elevated 17- hydroxyprogesterone (OHP) and/or androstenedione (A4) who were on stable glucocorticoid therapy over the preceding 6 months. Patients were randomised equally to receive oral hydrocortisone modified-release (n=61) or continue on their standard glucocorticoid therapy (n=61). The initial dose of hydrocortisone modified-release was equivalent to the baseline glucocorticoid dose with approximately one third of the daily dose taken at 7am and two thirds taken at 11pm. The starting dose of the standard glucocorticoid therapy was the same as that used prior to the study. Dose adjustments were conducted as necessary after 4 weeks and 12 weeks based on 24 hour 17-OHP and A4 profiles. Treatment was continued for 6 months after which patients could return to their standard glucocorticoid therapy or enter the DIUR-006 extension study. Efficacy analyses were performed in the efficacy evaluable set (EES) which comprised all patients who were randomised into the study, received at least one dose of study treatment, had an evaluable week 24 17-OHP 24-hour hormone profile, and had no major protocol violations.

The primary outcome for DIUR-005 was the change from baseline to 24 weeks in the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP. At the primary analysis, there was no statistically significant difference between treatment groups. Both groups achieved a negative change in the 17-OHP 24-hour standard deviation score profile indicating better hormonal control during the study. There were also no significant differences between treatment groups for any of the secondary outcomes. Results for the primary and secondary outcomes are presented in Table 1.

Table 1: Primary and key secondary outcomes from DIUR-005 in the EES population

	Hydrocortisone MR (N=53)	**Standard Glucocorticoid therapy (N=52)**
Change from baseline in 17-hydroxyprogesterone standard deviation score profile at 24-weeks		
Unadjusted mean change in 17-hydroxyprogesterone 24-hour profile from baseline to 24 weeks, mean (±SD)	-0.40 (±0.85)	-0.17 (±0.78)
LS mean change from baseline	-0.45	-0.38
Difference in LS means (95% CI)		-0.07 (-0.30 to 0.16), p=0.55
Change from baseline in androstenedione standard deviation score profile at 24-weeks		
Unadjusted mean change in androstenedione 24-hour profile from baseline to 24 weeks, mean (±SD)	0.11 (±0.92)	-0.04 (±0.77)
LS mean change from baseline	0.12	0.08
Difference in LS means (95% CI)		0.05 (-0.23 to 0.33)
17-hydroxyprogesterone and androstenedione levels at 9am as a responder analysis		
17-hydroxyprogesterone number of subjects with a response n, %	30 (57%)	30 (58%)
Adjusted response rate (%)	64%	64%
Odds ratio, 95% CI		0.99 (0.45 to 2.19), p=0.99
Androstenedione number of subjects with a response n, %	25 (47%)	26 (50%)
Adjusted response rate (%)	45%	47%
Odds ratio, 95% CI		0.93 (0.43 to 2.02), p=0.85

In the 24-hour 17-OHP curve, the early morning peak was reduced in the hydrocortisone modified-release group compared to the standard glucocorticoid group. In pre-planned exploratory analyses (not controlled for multiplicity) advised by the regulatory authority, a difference between treatment groups was observed in the 7am to 3pm 17-OHP profile in favour of hydrocortisone modified-release (difference in LS means: -0.29; 95% CI: [-0.56 to-0.01]) but not in the other 8 hour profiles and the area under the curve (AUC) for 17-OHP was also lower for hydrocortisone modified-release compared with standard glucocorticoid therapy group (difference in LS means: -13.77; 95% CI [-25.78 to 1.76]). There were differences identified between the groups measured by the lower limit and upper limit of the reference range for 17-OHP at baseline and week 24. [2]

DIUR-006 RCT

DIUR-006 is an ongoing long-term open-label extension study that recruited 91 patients who had completed DIUR-003 (phase II open-label pharmacokinetic study) or DIUR-005. Patients continued hydrocortisone modified-release or switched to hydrocortisone modified-release from standard glucocorticoid therapy. At the data cut-off 30 April 2019, there was a reduction in median daily dose from 30mg before the first titration period to 20mg during the 18-to-24-month period. There was also an increase in the percentage of patients achieving disease control (defined as 17-OHP levels at 9am within the optimal range), 57% at baseline (visit 1 of DIUR-006) to a maximum of 71% at week 12. [2]

Summary of safety data:

The total number of patients in the "pooled analysis" of the clinical trials programme was 120. Seventy-nine (79) of the 120 patients in the "pooled analysis" were exposed to Efmody® > 12 months including 43 subjects with an exposure duration > 24 months. [1]

In the clinical trial programme, the overall most common serious adverse events were acute adrenal insufficiency (4.2% of patients treated with Efmody®), fatigue (11.7% of patients), headache (7.5%), increased appetite (5.8%), dizziness (5.8%) and increased weight (5.8%).

The SPC for Efmody® lists the adverse drug reactions in the table below. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100):

Table 2. Tabulated summary of adverse reactions seen in clinical trial programme

MedDRA system organ classification	Event	Frequency
Endocrine disorders	Adrenal insufficiency including acute events	Common
Metabolism and nutrition disorders	Increased appetite	Common
	Decreased appetite	Common
	Impaired fasting glucose	Common
Psychiatric disorders	Insomnia	Common
	Abnormal dreams	Common
	Depressed mood	Common
	Sleep disorder	Common
Nervous System Disorders	Headache	Common
	Dizziness	Common
	Carpal tunnel syndrome	Common
	Paraesthesia	Common
Gastrointestinal disorders	Nausea	Common
	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Acne	Common
	Hair growth abnormal	Common

Musculoskeletal and connective tissue disorders	Arthralgia	Common
	Muscle fatigue/weakness	Common
	Myalgia	Common
	Pain in extremity	Common
General disorders and administration site conditions	Asthenia	Common
	Fatigue	Very Common
Investigations	Weight increased	Common
	Renin increased	Common

Efmody® is contraindicated in patients with hypersensitivity. The SPC also contains warnings about visual disturbances, growth retardation in adolescence, accelerated sexual maturation and decreased absorption in motility disorders. The SPC advises patients to swallow the capsules with water to wash the capsules down. The capsules should not be chewed as chewing the capsule could affect the release profile. [3]

Strengths and limitations of the evidence:

Strengths

- The EMA concluded that overall, the clinical characteristics of Efmody® treatment (delayed release effect mimicking physiological circadian rhythm, twice daily dosing, glucocorticoid sparing effect) were considered of added clinical value for patients. [1]
- The reported adverse events of Efmody® are considered to be in line with those known for oral hydrocortisone. [1]
- In the 24 hour 17-OHP curve early morning peak, a greater reduction was observed in the hydrocortisone modified-release group compared with standard glucocorticoid therapy. [2]
- A glucocorticoid sparing effect was seen in the overall population. In the long-term extension study, further dose reductions of Efmody® were possible without losing androgen control, suggesting a more optimal dosing. This finding is considered of additional clinical benefit for the patients, given the adverse consequences of long-term glucocorticoid treatment. [2]
- In their application for a new medicine, East Lancashire Hospitals trust suggested specific circumstances where Efmody® would be an appropriate second line treatment.

Limitations

- In study DIUR-005, there was no statistically significant difference observed between treatment groups for the primary endpoint and therefore clinical superiority of hydrocortisone modified-release versus standard glucocorticoid therapy in CAH patients has not been demonstrated. [2]
- There were a number of limitations associated with the study design and methodology of DIUR-005 including using the mean unsigned standard deviation score to measure the primary outcome. This approach cancels out circadian rhythms, is not sensitive to amplitude and does not separate effects above or below the normal mean. [2]
- There is a lack of evidence that has translated into clinical outcomes such as a clinically meaningful reduction in the effects of androgen excess on target tissues or steroid

sparing effects from over replacement. Body mass and bone density were measured as secondary outcomes but there was no difference between treatment groups.

- Due to the rareness of the condition, the study sample sizes are limited in the clinical trials programme.
- The Scottish Medicines Consortium do not recommend the use of Efmody® within NHS Scotland for the treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults because "The submitting company did not present sufficiently robust clinical and economic analysis to gain acceptance by SMC".

Summary of evidence on cost effectiveness:

The Scottish Medicines Consortium (SMC) carried out an economic analysis of Efmody®. Key findings are summarised in the tables below:

Table 3 - Base case results

Scenario number	Model assumption (Base-case)	Scenario	ICER at PAS price (£/QALY)
1	**Base-case results**		23,844
2	15% reduction in resource use due to hydrocortisone modified-release	No reduction in resource use due to hydrocortisone modified-release	24,310
3		10% reduction in resource use due to hydrocortisone modified-release	23,988
4	Treatment initiation at 12 years old	Treatment initiation at 18 years old	24,085
5	Falhammar et al. informs adrenal crisis mortality rate (3.9%)	Rushworth et al. informs adrenal crisis mortality (0.9%)	31,549
6		Hahner et al. informs adrenal crisis mortality (6.0%)	21,082
7	Cardiovascular disease - Sub model included	Cardiovascular disease - Sub model excluded	23,947
8	Obesity - Sub model included	Obesity - Sub model excluded	45,385
9	Fractures - Sub model included	Fractures - Sub model excluded	24,146
10	Due to a lack of evidence in children, patients under 18 years old were assumed to have the same risk of osteoporotic forearm fractures as 18-35 year olds.	No risk of forearm fractures associated with osteoporosis in patients under 18 years old	23,964
11	Diabetes - Sub model included	Diabetes - Sub model excluded	26,631
12	Fertility - Sub model included	Fertility - Sub model excluded	24,501
13	Height - Sub model included	Height - Sub model excluded	24,771
14	As stated in previous scenarios	All models - hormone control only	24,893
15		All models - glucocorticoids dosing impact only	70,734

Table 4 - Key scenario analysis results

Scenario number	Scenario	ICER at PAS price (£/QALY)
1	**Base-case results**	23,844
2	Time horizon: 5 years	63,886
3	Time horizon: 10 years	44,639
4	Time horizon: 20 years	33,519

5	Combined scenario with the following conditions: - Additional mortality risk is only included in the adrenal crisis sub-model - Exclusion of the diabetes sub-model - No reduction in resource use due to Hydrocortisone modified-release - Obesity - only glucocorticoid replacement therapy BMI increase associated with females, reflective of the CaHASE study - No risk of forearm fractures associated with osteoporosis in patients under 18 years old	34,236
6	Combined scenario with the following conditions: - Scenario 5 - 80% of patients receiving immediate release hydrocortisone and 20% receiving prednisolone - Rushworth et al. informs adrenal crisis mortality (0.9%)	49,263

Prescribing and risk management issues:

Treatment should be initiated by physicians experienced in the management of CAH.

As maintenance therapy the dose must be individualised according to the response of the individual patient. The lowest possible dose should be used.

Monitoring of the clinical response is necessary, and patients should be observed closely for signs that might require dose adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, changes in electrolytes particularly hypokalaemia, individual responsiveness to the medicinal product, and the effect of stress (e.g., surgery, infection, trauma). As the treatment has a modified-release profile, blood tests are used to monitor clinical response, assessment of the evening dose should be done with a morning blood test and assessment of the morning dose should be done with an early afternoon blood test.

During excessive physical and/or mental stress it may be necessary to increase the dose of Efmody®, and/or add additional immediate release hydrocortisone especially in the afternoon or evening.

Dose adjustments should be considered in case of concomitant use of potent CYP3A4 inducers or inhibitors. [3]

Commissioning considerations:

Innovation, need and equity implications of the intervention:

Hydrocortisone modified-release may benefit patients as it potentially improves disease control, reduces the total daily steroid dose, and has a convenient twice-daily administration. This could reduce disease-related symptoms and side effects associated with long-term steroid excess, patients may physically feel better and notice improvements in their mental health. The less rigorous dosing regimen of hydrocortisone modified-release is likely to improve compliance and have a positive impact quality of life of the patient, caregivers, and family members. Sleep is less likely to be disrupted for medication administration, compliance may improve with fewer doses required during the school or working day and social activities may be easier to plan. [2]

Financial implications of the intervention:

East Lancashire Hospitals Trust estimates that 5 patients will receive Efmody® in their trust. Assuming similar usage in other trusts in Lancashire and South Cumbria, it is estimated that 20 patients in Lancashire and South Cumbria would use Efmody® modified release capsules.

For Efmody® capsules:

Assuming a dose as follows:

- Adolescents aged 12 years and over who have not completed growth: 10mg to 15mg/m^2/day orally.
- Adolescents who have completed growth and adult patients: 15mg to 25mg/day orally.

The resulting annual cost of these doses would be **£2,948** to **£4,914**.

The total annual cost to treat 20 patients is **£58,960** to **£98,280**

For hydrocortisone 10 mg tablets:

Assuming the same dosing as above and c*osts for hydrocortisone 10mg tablets are based on using one tablet for each dose and assume wastage of the remainder of the tablet.*

2 to 3 tablets for 365 days = **£59** to **£88**

The total annual cost to treat 20 patients is **£1,180** to **£1,760.**

This would lead to a potential cost burden to the Lancashire and South Cumbria health economy of **£57,200** to **£97,100**.

Service Impact Issues Identified:

No service impact issues are expected for the supply of Efmody® capsules. Patients would continue to be initiated on treatment by specialists before prescribing responsibility is passed over to primary care clinicians. The reduced glucocorticoid burden and improved disease control are however likely to reduce access to other services such as fertility or diabetes services.

Equality and Inclusion Issues Identified:

No Equality issues are anticipated as this is an additional formulation of an existing treatment.

Cross Border Issues Identified:

Neither GMMMG nor Pan Mersey APC have a commissioning position on Efmody®. However, both areas have a “Black” RAG rating for the modified release tablet Plenadren.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

References

[1] European Medicines Agency, "Public Assessment Report Efmody (EMEA/H/C/005105/0000)," 2021.

[2] Scottish Medicines Consortium, "Hydrocortisone Modified-Release 5 mg, 10 mg and 20 mg Hard Capsules (Efmody)," 4 February 2022. [Online]. Available: https://www.scottishmedicines.org.uk/media/6729/hydrocortisone-modified-release-efmody-final-feb-2022-for-website.pdf. [Accessed 15 August 2022].

[3] E. M. Agency, "Annex I Summary of Product Characteristics," 27 May 2021. [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/efmody-epar-product-information_en.pdf. [Accessed 15 August 2022].

[4] SR Bornstein et al , "Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline," *Journal Clin Endocrinol Metab,* vol. 101, no. 2, pp. 364-389, 2016.

[5] PW Speiser et al, "Congenital Adrenal Hyperplasia due to Steroid 21 - Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline," *J Clin Endocrinol Metab,* vol. 95, no. 9, pp. 4133-4160, 2010.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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