Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2414

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

Diurnal Europe BV

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan equivalent medicine process

hydrocortisone modified-release (Efmody®) is not recommended for use within NHSScotland.

Indication under review: treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults.

In a phase III study, androgen suppression was similar with hydrocortisone modified-release compared with standard of care in adults.

The submitting company did not present sufficiently robust clinical and economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults.[1]

Dosing Information

The recommended replacement dose of hydrocortisone is 10 to 15mg/m^2/day in adolescents aged 12 years and over who have not completed growth, and 15 to 25mg/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.

Hydrocortisone modified-release capsules must be given orally. The capsules should not be chewed as this could affect the release profile. 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.

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

Further information including advice on changing from conventional glucocorticoid treatment, monitoring and dosing during serious trauma, intercurrent illness or periods of stress can be found in the summary product of characteristics (SPC).[1]

Product availability date

13 September 2021
Hydrocortisone modified-release capsules meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Hydrocortisone is a glucocorticoid and the synthetic form of endogenously produced cortisol. Glucocorticoids have salt-retaining and anti-inflammatory properties and have multiple effects in tissues through actions on the intracellular steroid receptors. Efmody® is a modified-release capsule formulation of hydrocortisone.[1]

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. Hydrocortisone stress dosing and fludrocortisone dose adjustment occurred as medically needed. Randomisation was stratified according to treatment at study entry (hydrocortisone only; prednisone or prednisolone, alone or in combination with hydrocortisone; or dexamethasone only or in combination with any other glucocorticoid). 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.[2, 3]

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.[2, 3]

Table 1: Primary and key secondary outcomes from DIUR-005 in the EES population[2, 3]

	Hydrocortisone MR (N=53)	**Standard GC therapy (N=52)**
Change from baseline in 17-OHP standard deviation score profile at 24-weeks		
Unadjusted mean change in 17-OHP 24 hour profile from baseline to 24 weeks[A], mean (±SD)	-0.40 (±0.85)	-0.17 (±0.78)
LS mean change from baseline[A]	-0.45	-0.38
Difference in LS means[B] (95% CI)	-0.07 (-0.30 to 0.16), p=0.55	
Change from baseline in A4 standard deviation score profile at 24-weeks		
Unadjusted mean change in A4 24-hour profile from baseline to 24 weeks[A], mean (±SD)	0.11 (±0.92)	-0.04 (±0.77)
LS mean change from baseline[A]	0.12	0.08
Difference in LS means[B] (95% CI)	0.05 (-0.23 to 0.33)	
17-OHP and A4 levels at 9am as a responder analysis[C]		
17-OHP number of subjects with a response[D] n,%	30 (57%)	30 (58%)
Adjusted response rate (%)	64%	64%
Odds ratio, 95% CI	0.99 (0.45 to 2.19), p=0.99	
A4 number of subjects with a response[D] n,%	25 (47%)	26 (50%)
Adjusted response rate (%)	45%	47%
Odds ratio, 95% CI	0.93 (0.43 to 2.02), p=0.85	

Changes in body composition (DEXA)		
Total fat mass LS mean change from baseline (kg)	-0.41	0.55
Difference in LS means, (95% CI)	-0.96 (-2.30 to 0.37)	
Total lean mass LS mean change from baseline (kg)	0.66	0.24
Difference in LS means, (95% CI)	0.43 (-0.46 to 1.31)	
Bone mineral density LS mean change from baseline (g/cm^2)	-0.01	-0.02
Difference in LS means, (95% CI)	0.01 (-0.01 to 0.03)	

17-OHP= 17-hydroxyprogesterone; A4=androstenedione; CI = confidence interval; DEXA = dual energy X-ray absorptiometry; EES = efficacy evaluable analysis set; GC=glucocorticoid; LS= least squares; MR=modified release
[A]A negative value indicates better hormonal control versus baseline. [B]A difference in LS means <0 favours modified-release hydrocortisone. [C]The number of patients achieving results in the optimal range at 9am at the week 24 visit. [D]Optimal range of 17-OHP = 1.2 to 36 nmol/L for males and 1.2 to 8.6 nmol/L for females. Optimal range for A4 = 1.4 to 5.2 nmol/L for males and 1.0 to 7.0 nmol/L for females.

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.[3, 4]

Health Related Quality of Life (HRQoL) was assessed using 36-item Short Form Health Survey (SF-36), Multidimensional Assessment of Fatigue and 5 Level Standardised Health Questionnaires. There were no significant differences between treatment groups at week 24 using any of the HRQoL instruments.[2]

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 on 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, 3]

Summary of evidence on comparative safety

A pooled safety analysis was conducted using data from DIUR-003, DIUR-005 and DIUR-006 (n=120) for the hydrocortisone modified-release group and DIUR-005 for the standard glucocorticoid group (n=61). Exposure to hydrocortisone modified-release in the pooled analysis

was ≥ 12months for 66% (79/120) of patients and ≥ 24 months for 36%. Any treatment related treatment emergent adverse events (TEAEs) were reported in 57% of patients in the hydrocortisone modified release group and 18% (11/61) in the standard glucocorticoid group.[3]

In the pooled hydrocortisone modified-release population compared with the DIUR-005 standard glucocorticoid group, the most frequent related TEAEs with an incidence of ≥5% included therapeutic response unexpected (22% versus 1.6%), fatigue (12% versus 8.2%), headache (8% versus 1.6%), increased appetite (5.8% versus 3.3%), dizziness (5.8% versus 1.6%), weight increased (5.8% versus 1.6%) and insomnia (3.3% versus 6.6%).[3]

In DIUR-005, 3 patients in the standard glucocorticoid therapy group and no patients in the hydrocortisone modified-release group reported adrenal crisis. In DIUR-006, 4 patients had an adrenal crisis, this was similar to population estimates in patients with adrenal insufficiency.[2]

Summary of clinical effectiveness issues

CAH is a group of inherited disorders that cause hyperandrogenism and adrenal insufficiency. Approximately 95% of CAH cases are caused by mutations in CYP21A2, the gene encoding adrenal steroid 21-hydroxylase. CAH due to 21-hydroxylase deficiency is divided into classic form (severe, early-onset) and non-classic form (mild, late-onset). Classic CAH is further subdivided into salt-wasting CAH (approximately two-thirds of patients) and simple-virilising CAH (one-third of patients.[3] Lack of 21-hydroxylase leads to cortisol deficiency and a counter-regulatory increase in pituitary adrenocorticotropin secretion, which drives overproduction of adrenal androgens and adrenal hyperplasia. Adrenal insufficiency can cause asthenia, low blood pressure, electrolyte disturbance and risk of life threatening adrenal crises under conditions of physical or emotional stress. Androgen excess can cause atypical genitalia in female neonates, promotion of abnormal growth, short stature and precocious puberty. In adulthood, it can cause virilisation of women and infertility in both sexes. Clinical guidelines recommend immediate-release hydrocortisone as first-line treatment for CAH in patients of all ages. Prednisolone, prednisone or dexamethasone may be suitable second line treatment options in selected adult patients. To overcome the disadvantages of the available therapies, particularly, the lack of control of the early morning peak in androgen levels, new treatment approaches and glucocorticoid formulations are needed that mimic the circadian rhythm of physiological adrenocortical secretion. CAH is a rare condition; in Great Britain, the point prevalence is estimated to be approximately 0.8 in 10,000.[2, 4, 5] Hydrocortisone modified-release meets SMC orphan equivalent criteria for this condition. Clinical experts consulted by SMC considered that hydrocortisone modified-release fills an unmet need for this indication as currently the disease may be poorly controlled with the available treatment options.

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. There were also no significant between group differences for secondary outcomes. 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. A number of post hoc analyses were conducted that were considered clinically relevant and supportive of the efficacy of hydrocortisone modified-release by the European Medicines Agency (EMA). In extension study DIUR-006, an increased proportion of patients achieved disease control with further clinically meaningful dose reductions possible.[2, 3]

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. The primary analysis was also hampered by the strict titration regimen based on 24 hour 17-OHP levels, which is unlikely to be carried out in clinical practice. 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. The DIUR-005 study duration (6 months) may have been adequate to assess the effect of hydrocortisone modified-release on biomarkers however CAH is a lifelong condition and longer-term follow-up is required for clinical outcomes. DIUR-006 extension study is ongoing.[2-4] The sample sizes are limited, DIUR-005 included 122 patients, DIUR-006 included 91 patients and the safety analysis included 138 patients. The open-label study design may have introduced bias to subjective outcomes such as safety and HRQoL.

DIUR-005 and DIUR-006 included patients aged ≥ 18 years, however, the EMA agreed that, from a clinical perspective, it was acceptable to extrapolate the data to adolescents aged 12 to 17 years.[3]

Clinical experts consulted by SMC considered hydrocortisone modified-release would be used particularly in patients with poorly controlled symptoms, abnormal biochemistry or on frequent dosing regimens.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **hydrocortisone modified-release capsules**, as an **orphan-equivalent** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Congenital adrenal hyperplasia (CAH) is a rare chronic condition characterised by cortisol deficiency and androgen excess. The disease ranges in severity and can be difficult to manage. Excess androgen levels promote abnormal growth, short stature, acne, hirsutism, virilisation in females and infertility in both sexes. Cortisol deficiency can cause light-headedness, affect concentration and patients may feel lethargic with no energy to do 'normal' everyday things that others take for granted. If levels are too low they are at risk of life-threatening adrenal

crisis. These disease-related symptoms have a significant physical and psychological impact on the patient.

- Patients require long-term treatment with glucocorticoids. First-line treatment is with immediate-release hydrocortisone and high doses with complex administration regimens are often needed to suppress androgens and mimic the cortisol circadian rhythm. Very late night and early morning dosing often disrupts sleep and the dosing frequency means that medication has to be taken at work or administered at school for younger patients. Impractical dosing regimens can reduce compliance, which leads to poor control with the risk of adrenal crisis, infertility and other symptoms of androgen excess.
- 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.
- With improved disease control, fewer outpatient appointments may eventually be required for biochemical testing. This could reduce disruption to education and work associated with attending appointments. Better control may also reduce hospital admissions caused by adrenal crisis.
- PACE participants agreed that hydrocortisone modified-release would be most likely to be of benefit for those struggling to achieve good control with current formulations.

Additional Patient and Carer Involvement

We received a patient group submission from the CAH Support Group, which is a registered charity. The CAH Support Group has not received any pharmaceutical company funding in the past two years. A representative from the CAH Support Group participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating the use of hydrocortisone modified-release within its full licensed indication. The analysis compared hydrocortisone modified-release with glucocorticoid replacement therapy consisting of a mix of immediate-release hydrocortisone, prednisolone and dexamethasone. Adult patients were allocated to the respective glucocorticoid replacement therapies; 75%, 20% and 5% respectively. For adolescents in the model, 85% were allocated to immediate-release hydrocortisone and 15% to prednisolone with no adolescent receiving dexamethasone. The majority of SMC clinical experts indicated only hydrocortisone and prednisolone were relevant comparators.

A de-novo cohort-level cost utility model was used to represent co-morbidities associated with CAH using seven sub models; adrenal crises, cardiovascular disease, fractures, obesity, fertility, diabetes and height. Patients entered the model at 12 years old and were able to enter multiple sub-models in each cycle. The model had a cycle length of 1 month and a time horizon of 88 years with a maximum patient age of 100 as patients were assumed to receive treatment for the remainder of their lifetime.

Clinical inputs for the probabilities of a patient experiencing events in each sub-model were taken from various published literature and DIUR-006 data was applied in the adrenal crisis sub-model with relative risks being applied to the different treatment arms.[2] The submitting company also relied on clinical interviews with clinical experts for validation and opinions. The interviews were conducted with 7 clinical experts. 3 were from Sweden, 1 Norway, 1 Italy and 2 Scotland. Three worked with adults and adolescents, 2 adults only and 2 adolescents only. The views and assumptions expressed by the experts were not always adhered to by the company, and there was uncertainty as to whether the obesity and diabetes sub-models should have been included. Clinical inputs for these sub-models have been presented below in Table 2.

Table 2. Risks applied in sub-models[6-10]

Sub-model	Hydrocortisone modified-release	Assumption/source	Glucocorticoid steroid replacement	Assumption/source
Obesity	CAH patients had a BMI 1.23 times that of the general population for patients who were receiving more than 20mg of hydrocortisone per day by 0.2 units	CaHASE study (though values were for females only – company assumed equal rates for men in model) Burning et al. (2017)	CAH patients had a BMI 1.23 times that of the general population for patients who were receiving more than 20mg of hydrocortisone per day by 0.2 units	CaHASE study (though values were for females only – company assumed equal rates for men in model) Burning et al. (2017)
	HR of 1.01 for every BMI unit above 27.4kg/m^2 applied for cancer related mortality	Wade et al. (2018)	HR of 1.01 for every BMI unit above 27.4kg/m^2 applied for cancer related mortality	Wade et al. (2018)
Diabetes	Equal of the general population risk	Company assumption	Increased odds ratio of diabetes in CAH patients compared with age-matched controls (OR = 3.0 [CI 1.6, 5.8]).	Falhammar et al. (2015).

	Elevated mortality risk associated with diabetes with a HR of 1.8	Seshasai et al. (2014)	Elevated mortality risk associated with diabetes with a HR of 1.8	Seshasai et al. (2014)

Quality of life data were collected in DIUR-005 with no difference in EQ-5D score changes from baseline between the two treatment arms.[2] In DIUR-006 there were also no significant differences in EQ-5D scores from baseline to each visit. This may indicate that any utility difference between treatment arms is uncertain. The utilities assigned to the outcome in the co-morbidity sub-models were based on literature values only. The impact of the comorbidity on health-related quality of life and mortality relative to the age-adjusted general population values was estimated and multiplied by the proportion of patients experiencing an event of interest in each cycle. These values were combined multiplicatively to estimate overall utility and mortality multipliers, which were then applied to the age-related utility values and mortality rates in that cycle.

Medicine costs included were acquisition costs and concomitant medication costs. No administration costs or adverse event costs were applied. The list price of hydrocortisone modified-release was £0.54 per mg.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. The base case and sensitivity analysis results are shown below in table 3.

The submitting company also performed a one-way sensitivity analysis where the risk of obesity was the most influential parameter. A number of key scenarios are summarised in table 3, however additional scenarios were requested from the submitting company presented in Table 4. The key sensitivities included the inclusion or exclusion of the obesity sub-model, the adrenal crisis mortality rate and glucocorticoids dosing impact only on risk of sub-model events.

Table 3: Base case and scenario analysis – key 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

Scenario number	Model assumption (Base-case)	Scenario	ICER at PAS price (£/QALY)
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

ICER = incremental cost-effectiveness ratio, PAS = patient access scheme, QALY = quality-adjusted life-year

Table 4. Requested scenario analyses

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	49,263

Scenario number	Scenario	ICER at PAS price (£/QALY)
	and 20% receiving prednisolone - Rushworth et al. informs adrenal crisis mortality (0.9%)	

ICER = incremental cost-effectiveness ratio, PAS = patient access scheme, QALY = quality-adjusted life-year, BMI = body mass index

Key weaknesses:

- No clinical data from DIUR-005 were used in the model, and only the adrenal crisis data from DIUR-006 were used. Much of the clinical evidence was based on clinical opinions and various literature sources, making it highly uncertain. Many assumptions also contradicted the non-statistically significant findings from DIUR-005. The Committee also noted that the relatively large life-year and QALY gains with hydrocortisone modified-release estimated in the model lacked face validity when compared with the clinical evidence presented.
- Due to the lack of clinical data underpinning the economic model assumptions, a cost-comparison model was provided as it may be a more appropriate approach. This showed a significant incremental cost with hydrocortisone modified-release.
- Based on literature and previous submissions, the model may include too many health effects and sub-models, potentially double counting various health effects and biasing the results in favour of hydrocortisone modified-release.
- Despite the clinical interviews, the submitting company did not always adhere to the majority view of the experts and have included values in favour of hydrocortisone modified-release. Alternative scenarios rectifying for this were requested.
- There was a lack of available evidence for the adolescent population and as a result the submitting company included assumptions based on clinical opinions only for this population. Results excluding adolescents may be preferred based on available evidence.
- Based on the literature referenced by the submitting company, it may only be appropriate to add mortality risk to the adrenal crisis sub-model. The submitting company provided a combined scenario excluding the additional mortality risks in the model.
- The submitting company stated that the utility decrement and relevance to adult CAH patients experiencing adrenal crisis had been validated by clinical experts. In the reports presented by the company, however, there was no indication that they were presented with individual utility decrements applied, but instead just the total end utility values, and it is uncertain that they did in fact validate this disutility as suitable.
- It was assumed that resource use in the hydrocortisone modified-release arm was reduced by 15%. The company justified this due to the likely improved patient adherence and elimination of sampling and disease monitoring as disease control would be optimal. This cost reduction was based solely on expert interviews, during which they also highlighted that the way they interacted had changed to a more virtual way during the Covid-19 pandemic. There is little data underpinning this assumption, and a combined scenario was provided where this assumption is omitted.

The Committee considered the benefits of hydrocortisone modified-release in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as hydrocortisone modified-release is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept hydrocortisone modified-release for use in NHSScotland.

Additional information: guidelines and protocols

The (US) Endocrine Society[5], endorsed by the European Society of Endocrinology and European Society for Paediatric Endocrinology, published guidelines in 2018 and made the following recommendations. In children with CAH, maintenance therapy with hydrocortisone 10–15mg/m^2/day divided into two or three doses is recommended. Hydrocortisone is the preferred glucocorticoid for the treatment of growing individuals with CAH, because it's short half-life minimises the adverse effects typical of longer-acting more potent glucocorticoids, especially growth suppression. In adults with CAH, there is no consensus on optimal treatment. Daily hydrocortisone and/or long-acting glucocorticoids as replacement therapy are recommended. With regards to monitoring adults with CAH the recommendation is for monitoring treatment through consistently timed hormone measurements relative to medication schedule and time of day. In adults with CAH it is recommended that clinicians do not completely suppress endogenous adrenal steroid secretion to prevent adverse effects of overtreatment.

Additional information: comparators

Immediate-release hydrocortisone, prednisolone and dexamethasone.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Hydrocortisone modified-release capsules	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.	2,948 to 4,914

Costs from MIMS online on 03/11/21. 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.

Additional information: budget impact

The submitting company estimated there would be 263 patients eligible for treatment with Hydrocortisone modified-release in each year 1 and 274 patients in Year 5. The estimated uptake rate was 4% in year 1 and 60% in year 5. This resulted in 11 patients estimated to receive treatment in year 1 rising to 164 patients in year 5.

Based on the list price the gross medicines budget impact was estimated to be £57k in year 1 rising to £789k in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £54k in year 1 rising to £743k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 10 December 2021.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.