NHS
Vale of York
Clinical Commissioning Group

COMMISSIONING POLICY RECOMMENDATION
TREATMENT ADVISORY GROUP
Policy agreed by (*Vale of York CCG/date*)

Drug, Treatment, Device name		
Hydrocortisone Modified Release Tablets ▼ Plenadren®, (ViroPharma) Available as 5mg and 20mg tablets.		
Licensed indication		
Treatment of adrenal insufficiency in adults.		
Cost per patient (at recommended dose)		
Plenadren▼	20mg to 30mg daily	20mg - £224 30mg - £495.60 (28 days)
Prednisolone	5mg daily	£3.14 (28 days)
Hydrocortisone IR	20mg daily (in divided doses)	60x10mg tabs = £100.88 (30 days)
Dexamethasone	750mcg daily	84 x 500mcg tabs = £144 (28 days)
Resource impact on population		
Adrenal insufficiency (AI) is a rare condition with a prevalence of 2 to 4 per 10,000 people.		
Recommendation to Routinely Commission **OR** **Not Routinely Commission** **OR** **Commission under criteria**		
When is funding appropriate?		
Plenadren® is not recommended for the treatment of adults with adrenocortical insufficiency. Robust evidence of a clear therapeutic advantage to justify the significantly greater acquisition costs compared with Immediate Release Hydrocortisone is currently lacking.		
Clinical and cost effectiveness evidence		

Background

Adrenal Insufficiency leads to deficiency of glucocorticoid and in some cases, mineralocorticoid hormones. It can be primary (where the adrenal glands fail to produce enough steroid hormones, as in Addison's disease) or secondary (where the pituitary gland or hypothalamus do not adequately stimulate the adrenal glands). It can be fatal if untreated, and patients will require lifelong replacement.
The most common glucocorticoid used is immediate release hydrocortisone, in daily doses of 15mg to 30mg. Ideally it should e taken three times day, but is sometimes given in two divided doses with two thirds in the morning. There are no objective measures to assess effectiveness of treatment and doses are adjusted according to clinical response. Over and under replacement need to be avoided as both are associated with increased morbidity and mortality.

UKMI New Medicines Profile Oct 2012
Summary
- Plenadren® is an oral modified-release formulation of hydrocortisone licensed to treat adults with adrenal

insufficiency (AI).
• Although designed to more closely mimic natural cortisol release than current glucocorticoids, Plenadren® only partly achieves this.
• The amount of hydrocortisone absorbed systemically from Plenadren® is about 20% less than from immediate-release (IR) hydrocortisone. Although this could be beneficial in some patients (over-substitution with current glucocorticoids is common), for others on lower doses (20mg daily or less), it could lead to under-substitution.
• Mean body weight and blood pressure were reduced to a small extent after 12 weeks' treatment with Plenadren® compared with the same dose of hydrocortisone IR. A trial comparing Plenadren® with a 20% lower daily dose of hydrocortisone IR is needed to show whether these metabolic effects could be achieved by reducing the dose of hydrocortisone IR.
• There is no evidence that Plenadren's® concentration-time profile and the short-term changes in some surrogate measures of disease reduce morbidity or mortality.
• Patients prefer Plenadren® once daily to hydrocortisone IR taken three times a day but compliance with the two formulations is similar. Quality of life data are difficult to interpret and should be viewed with caution as they come from open-label studies with small numbers of patients.
• Plenadren® and hydrocortisone IR cause similar adverse effects of abdominal pain, diarrhoea, nausea and fatigue. However, patients switched to Plenadren® may feel less well for the first few months as they adjust to the change in cortisol levels.
• Prescribers should make sure patients with AI take the lowest effective dose of glucocorticoid – a daily hydrocortisone dose of 15 to 20mg is adequate for most adults with primary AI.
• Plenadren® is an option for patients with poor compliance, but its use will significantly increase the cost of therapy. Patients should be monitored closely when switching to avoid under-substitution.

NMP Hydrocortisone MR.1.pdf

J Clin Endocrinol Metab. 2012 Feb;97(2):473-81. doi: 10.1210/jc.2011-1926. Epub 2011 Nov 23.

Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation.

Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, Engström BE, Olsson T, Ragnarsson O, Ryberg M, Wahlberg J, Biller BM, Monson JP, Stewart PM, Lennernäs H, Skrtic S.
Source
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Abstract

CONTEXT:
Patients with treated adrenal insufficiency (AI) have increased morbidity and mortality rate. Our goal was to improve outcome by developing a once-daily (OD) oral hydrocortisone dual-release tablet with a more physiological exposure-time cortisol profile.
OBJECTIVE:
The aim was to compare pharmacokinetics and metabolic outcome between OD and the same daily dose of thrice-daily (TID) dose of conventional hydrocortisone tablets.
DESIGN AND SETTING:
We conducted an open, randomized, two-period, 12-wk crossover multicenter trial with a 24-wk extension at five university hospital centers.
PATIENTS:

The trial enrolled 64 adults with primary AI; 11 had concomitant diabetes mellitus (DM).
INTERVENTION:
The same daily dose of hydrocortisone was administered as OD dual-release or TID.
MAIN OUTCOME MEASURE:
We evaluated cortisol pharmacokinetics.
RESULTS:
Compared with conventional TID, OD provided a sustained serum cortisol profile 0-4 h after the morning intake and reduced the late afternoon and the 24-h cortisol exposure. The mean weight (difference = -0.7 kg, P = 0.005), systolic blood pressure (difference = -5.5 mm Hg, P = 0.0001) and diastolic blood pressure (difference: -2.3 mm Hg; P = 0.03), and glycated hemoglobin (absolute difference = -0.1%, P = 0.0006) were all reduced after OD compared with TID at 12 wk. Compared with TID, a reduction in glycated hemoglobin by 0.6% was observed in patients with concomitant DM during OD (P = 0.004).
CONCLUSION:
The OD dual-release tablet provided a more circadian-based serum cortisol profile. Reduced body weight, reduced blood pressure, and improved glucose metabolism were observed during OD treatment. In particular, glucose metabolism improved in patients with concomitant DM

Points for consideration

- Limited data on the pharmacokinetics (PK), efficacy and safety of Plenadren® in primary AI are available from one phase II/III randomised cross-over study. There are no studies involving patients with secondary AI.
- Though patients are likely to prefer to take a once daily preparation, compliance with the two two formulations is similar. Adherence to treatment is high in patients with AI, since non-compliance causes uncomfortable symptoms.
- There is no evidence that Plenadren's concentration-time profile and the short term changes in some surrogate measures of disease reduce morbidty or mortality.
- It is unlikely that plenadren would be a cost effective treatment option for this condition compared to IR hydrocortisone.

Place in therapy relative to available treatments

Plenadren® is an option for patients with poor compliance, but its use will significantly increase the cost of therapy. Patients should be monitored closely when switching to avoid under-substitution.

Health gains

Potentially increased compliance however, this is in a patient group whose compliance is usually high.

Patient safety / pharmacovigilance

The frequency and type of adverse reactions were similar for Plenadren once daily modified-release tablets and hydrocortisone tablets given three times daily in a 12-week study. There was an initial increase in the frequency of adverse reactions in about one in five patients, observed up to eight weeks after first changing from conventional hydrocortisone tablets given three times daily to once daily modified-release tablets. However, these adverse reactions (abdominal pain, diarrhoea, nausea and fatigue) are mild or moderate, transient, of short duration but may require dose adjustment or additional concomitant medicinal products. Fatigue has been reported as very common.

When to stop treatment

N/A

Who prescribes?

Plenadron is not recommended.

Stakeholder views
HaRD APC – Plenadron was not approved.
Equity of access

SPECIFICATION DATE, REVIEW DATE, AND LEAD NAME/JOB TITLE	
Origin Date:	Originator:
TAG Review Date:	
TAG Recommendation Date:	

Impact on individual clinical commissioning groups		
CCG	**Population**	**Cost Impact**
York	337,500	£52,520.40
HaRD	160,100	£24,914
Scarborough	118000	£18,362.68
H&R	141,600	£22,035.26
East Riding	302,000	£46,996
Hull	295,987	£46,684
North Lincs	168,400	£26,205.73
North East Lincs	167,200	£26,019

The above assumes a prevalence of 2 per 10,000 population and patients taking a dose of plenadron 20mg daily and has been offset from annual cost of immediate release hydrocortisone (20mg daily – divided doses).