Lancashire Medicines Management Group NHS

LMMG New Medicine Recommendation

Hydrocortisone MR (Plenadren® ▼)

LMMG Recommendation: Black

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.

Summary of supporting evidence:

- Plenadren® is an oral modified-release formulation of hydrocortisone licensed to treat adults with adrenal insufficiency (AI)
- It is designed to more closely mimic natural cortisol release than current glucocorticoids but only partly achieves this.
- The amount of hydrocortisone absorbed systemically from Plenadren® is approximately 20% less than from immediate release hydrocortisone.
- Mean body weight and blood pressure were reduced to a small extent after 12 weeks treatment with Plenadren® compared to immediate release hydrocortisone. A trial comparing Plenadren® with a 20% lower daily dose of immediate release hydrocortisone is needed to show whether these metabolic effects could be achieved by reducing the dose of immediate release hydrocortisone.
- 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 immediate release (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

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Version:	**LMMG Recommendation**
Reviewer	**Brent Horrell**
Clinical Reference Group (if appropriate)	
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Date of recommendation to member organisations by LMMG:	**11th July 2013**

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Details of Review

Name of medicine (generic & brand name)**:** Hydrocortisone MR (Plenadren® ▼)
Strength(s) and Form(s): 5mg and 20mg tablets
Licensed indication(s): Treatment of adrenal insufficiency in adults[3]
Reason for Review: Identified by East Lancashire CCG as a product which could result in a significant cost pressure.
Proposed use (if different from or in addition to licensed indication above): In line with the licensed indication

Background and context

Adrenal Insufficiency is a rare condition with a prevalence of 2 to 4 per 10,000 people, which leads to deficiency of glucocorticoid and, in some cases, mineralocorticoid hormones. Adrenal Insufficiency 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).[4]

The most common glucocorticoid used to treat Adrenal Insufficiency is immediate-release (IR) hydrocortisone, in daily doses of 15mg to 30mg. Ideally it should be taken three times a day (e.g. 10mg on waking, 5mg at noon and 5mg in the early evening), but is sometimes given in two divided doses with two thirds in the morning.[4]

Longer-acting prednisolone or dexamethasone are sometimes used because of improved patient convenience but, unlike hydrocortisone, have no mineralocorticoid activity. However, accurate replacement of physiological diurnal and pulsatile ultradian cortisol levels is impossible with currently available glucocorticoids.[4]

Plenadren® is an oral modified-release formulation of hydrocortisone designed to more closely mimic the natural cycle of cortisol release than current glucocorticoids. It has a slow-releasing inner core surrounded by an outer layer which quickly releases hydrocortisone.[5]

Evidence in Proposed Use

This evidence review draws largely on the UKMI New Medicines Profile: Hydrocortisone modified-release. Issue Mo. 12/01, October 2012[4]

Summary of Efficacy Data in Proposed Use:

In the main cross-over study, 64 adults on stable doses of hydrocortisone IR (20-40mg daily) were randomised to a single dose of Plenadren® before breakfast, or hydrocortisone IR taken in three divided doses at 8am (before food), 12pm and 4pm for 12 weeks. Patients were immediately switched to the same (mg for mg) dose of the alternative formulation for a further 12 weeks, before they were all given Plenadren® for an additional six months (n=59).[4]

The primary outcome was serum cortisol exposure-time profile. Plenadren® treatment resulted firstly in a high peak of serum cortisol after the morning dose, and then a slow, smooth decline during the afternoon, with negligible levels overnight; three peaks after each dose were observed with hydrocortisone IR. Mean total serum cortisol area under the curve (AUC0-24h) was 19.4% lower with Plenadren® vs. hydrocortisone IR.

In comparison with the natural cortisol cycle, Plenadren® achieves higher morning levels but lower afternoon and evening levels; it does not mimic the gradual cortisol increase before awakening, the two daytime spikes associated with eating or the frequent pulses. Therefore, Plenadren® only partly mimics the physiological profile of cortisol. The CHMP noted that the lower bioavailability of Plenadren® could be potentially beneficial for some patients as over-substitution is an important drawback of current glucocorticoid therapy. However, avoiding over-substitution could also be achieved by reducing the prescribed hydrocortisone IR dose.[4]

In the trial, mean body weight and blood pressure decreased slightly over 12 weeks' treatment with Plenadren®, but increased with hydrocortisone IR; the difference between the groups was statistically significant.[4] These data are not sufficient to support an improved metabolic profile; longer-term data and a trial comparing Plenadren with a 20% lower dose of hydrocortisone IR are needed.[4]

Summary of Safety Data:

The EU Committee for Medicinal Products for Human Use (CHMP) assessed limited safety data from a total patient exposure of about 145 patient-years. The frequency and type of adverse effects (AEs) are similar with Plenadren® and hydrocortisone IR, and include fatigue, abdominal pain, diarrhoea and nausea. Patients taking Plenadren® report AEs more commonly during the first eight weeks of treatment, especially fatigue. This may indicate a relative under-substitution when changing from hydrocortisone IR to the same dose of Plenadren® because patients may have previously been taking too high a dose. The CHMP state that this is not expected to be a problem in clinical practice, as AE rates decline with continued use.
However, the possibility of under-substitution when switching to Plenadren® should be considered in all patients and especially those on daily doses of 20mg or less.
Plenadren® is not recommended for patients with increased gastrointestinal motility; such patients were excluded from clinical studies as absorption of hydrocortisone may be affected.

Summary of Evidence on Cost Effectiveness and Patient Outcomes:

Data from three validated quality of life (QoL) questionnaires showed Plenadren® use resulted in a slight decrease in scores of borderline significance at four weeks, especially in physical wellbeing. At 12 weeks this was less pronounced and there was an improvement in psychosocial domains.

Initial decreases may be caused by transient hypocortisolism. Energy, measured using an un-validated diurnal fatigue scale, showed an improvement only with Plenadren®. There was little change after a further 6 months.
However these QoL data should be interpreted cautiously; bias is possible because the trial was not blinded. 85% of patients preferred Plenadren® to hydrocortisone IR. Also, before the study 55% of patients were taking hydrocortisone IR twice daily, so the influence of a switch to three times daily dosing is unknown.

Key Points to Note from the Available Evidence:

- Plenadren® is designed to more closely mimic natural cortisol release than current glucocorticoids but only partly achieves this.
- The amount of hydrocortisone absorbed systemically from Plenadren® is approximately 20% less from immediate release hydrocortisone.
- Mean body weight and blood pressure were reduced to a small extent after 12 weeks treatment with Plenadren® compared to immediate release hydrocortisone. A trial comparing Plenadren® with a 20% lower daily dose of immediate release hydrocortisone is needed to show whether these metabolic effects could be achieved by reducing the dose of immediate release hydrocortisone.
- 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 immediate release (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

Innovation, Need and Equity Considerations:

Plenadren® is an oral modified-release formulation of hydrocortisone licensed to treat adults with adrenal insufficiency. It is taken once daily, which may be of greater convenience to patients however 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

There are no anticipated equity considerations.

Recommended Place in Therapy

Plenadren® is not recommended in the treatment of adults with adrenocortical insufficiency.

The use of Plenadren® would lead to a significant cost pressure. While some surrogate measures improved in patients on Plenadren® it is unclear how Plenadren® would compare to a 20% dose decrease in immediate release hydrocortisone. It is also unclear if these surrogate measure changes reduce disease morbidity or mortality.

Both SMC[1] and AWMSG[2] have not endorsed the use of Plenadren®. Their respective decisions were taken in the absence of any submissions from the holder of the marketing organisations and for AWMSG in light of NICE proposing to publish guidance within 12 months (but not currently listed).

Financial and Service Implications

Comparative unit costs:

Drug name	**Example regimen**	**Pack cost**	**Annual maintenance cost per patient (ex VAT)**
Hydrocortisone MR (Plenadren®)	**20mg – 30mg (1 x 20mg + 2 x 5mg) Daily**	**50 x 5mg = £242.50** **50 x 20mg = £400.00**	**£2,920 - £6,461**
Hydrocortisone Immediate Release (Non-proprietary)	20mg – 30mg daily Given as a larger dose in the morning and smaller in the afternoon)	30 x 10mg = £49.63 30 x 20mg = £51.07	£621 - £1,225

Anticipated patient numbers and net budget impact:

Based on ePACT data for Q4 (2012-13) the current annual expenditure on Hydrocortisone across Lancashire is likely to be £1.2million (0.5% of this is already Plenadren®). If all prescribing was switched to Plenadren® there would be an annual increase in acquisition costs of £4.5 million - £5.2 million.

Impact on service delivery to patients:

No impact on service delivery is expected.

References

1. http://www.scottishmedicines.org.uk/SMC_Advice/Advice/848_12_hydrocortisone_Plenadren/hydrocortisone_Plenadren
2. Hydrocortisone MR (Plenadren®) for the treatment of adrenal insufficiency in adults, ViroPharma Ltd, February 2012 Statement of Advice – All Wales Medicines Strategy Group.
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4. UKMi New Medicines Profile: Hydrocortisone modified-release. Issue Mo. 12/01, October 2012
5. Plenadren, European Public Assessment Report Scientific discussion. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002185/human_med_001495.jsp&mid=WC0b01ac058001d124 Accessed 29/5/2013
6. Eisen SA, Miller DK, Woodward RS et al. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990; 150: 1881-4.
7. McKenna TJ. Addison's disease. Last updated Apr 2013. BMJ Best Practice. Available at: http://bestpractice.bmj.com/ Accessed 29/5/2013.

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