TRANSPARENCY COMMITTEE
Opinion
5 March 2014

PLENADREN 5 mg, modified-release tablet,
Bottle of 50 tablets (CIP: 34009 266 249 0 3)
PLENADREN 20 mg, modified-release tablet,
Bottle of 50 tablets (CIP: 34009 266 250 9 2)

Applicant: VIROPHARMA

<table>
<thead>
<tr>
<th>INN</th>
<th>Hydrocortisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2012):</td>
<td>H02AB09 (Corticosteroids for systemic use - Glucocorticoids)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
<tr>
<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
</tr>
<tr>
<td></td>
<td>Hospital use (French Public Health Code L.5123 2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>&quot;Treatment of adrenal insufficiency in adults.&quot;</td>
</tr>
<tr>
<td>Actual Benefit</td>
<td>The actual benefit of PLENADREN is substantial.</td>
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<tr>
<td>Improvement in Actual Benefit</td>
<td>The PLENADREN modified-release dosage form of hydrocortisone is closer to the pharmacokinetic profile of the physiological rhythm of cortisol, without any clinical consequence having been demonstrated. Consequently, PLENADREN provides a minor improvement in actual benefit (IAB IV) in the care of patients with adrenal insufficiency.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>Glucocorticoids are first-line therapies. PLENADREN is a new proprietary medicinal product based on hydrocortisone administered orally, with a modified-release dosage form that represents an alternative to immediate-release HYDROCORTISONE ROUSSEL.</td>
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<td>Recommendations</td>
<td></td>
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# 01 ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>The Marketing Authorisation is associated with a request for additional clinical studies (see section 8.4) and a risk management plan (RMP).</td>
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</table>

<table>
<thead>
<tr>
<th>Prescribing and dispensing conditions/special status</th>
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<tbody>
<tr>
<td>List I Orphan medicinal product</td>
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</table>

<table>
<thead>
<tr>
<th>ATC Classification</th>
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<tbody>
<tr>
<td>2012</td>
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<tr>
<td>H</td>
</tr>
<tr>
<td>H02</td>
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<tr>
<td>H02A</td>
</tr>
<tr>
<td>H02AB</td>
</tr>
<tr>
<td>H02AB09</td>
</tr>
<tr>
<td>Systemic hormonal preparations, excl. sex hormones and insulins</td>
</tr>
<tr>
<td>Corticosteroids for systemic use</td>
</tr>
<tr>
<td>Corticosteroids for systemic use, plain</td>
</tr>
<tr>
<td>Glucocorticoids</td>
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<tr>
<td>hydrocortisone</td>
</tr>
</tbody>
</table>

# 02 BACKGROUND

This concerns a request for inclusion on the list of medicinal products refundable by National Health Insurance and approved for hospital use for the proprietary medicinal product PLENADREN (hydrocortisone) which obtained a Marketing Authorisation on 3/11/2011 accompanied by a request for an additional clinical study to evaluate the safety and efficacy of PLENADREN based on:

- setting up a prospective European multicentre registry for patients with chronic adrenal insufficiency,
- a retrospective study to evaluate the prescription conditions for PLENADREN from Swedish registries.

PLENADREN is a proprietary medicinal product based on hydrocortisone developed with a new dosage form, a modified-release tablet.

# 03 THERAPEUTIC INDICATION

"Treatment of adrenal insufficiency in adults"

# 04 DOSAGE

"Posology
PLENADREN is given as maintenance therapy. Oral replacement doses must be individualised according to the clinical response. A common maintenance dose is 20 – 30 mg of PLENADREN per day, given once daily in the morning. In patients with some remaining endogenous cortisol production a lower dose may be sufficient. 40 mg is the highest maintenance dose of PLENADREN studied. The lowest possible maintenance dosage should be used. In situations when the body is exposed to excessive physical and/or mental stress, patients may need additional substitution of immediate release hydrocortisone tablets especially in the afternoon/evening, see also section 'Use in intercurrent illness' where other ways of temporarily increasing the dose of hydrocortisone are described."
Changing from conventional oral glucocorticoid treatment to PLENADREN

When changing patients from conventional oral hydrocortisone replacement therapy given three times daily to PLENADREN, an identical total daily dose may be given. Due to a lower bioavailability of the daily dose of PLENADREN compared to that of conventional hydrocortisone tablets given three times daily (see section 5.2) clinical response needs to be monitored and further dose individualisation may be required. Changing patients from hydrocortisone tablets given twice daily, cortisone acetate or synthetic glucocorticoids to PLENADREN has not been studied, but changing to a hydrocortisone equivalent daily dose of PLENADREN is recommended in these instances; further dose individualisation may be required.

Use in intercurrent illness

During intercurrent illness, there should be high awareness of the risk of developing acute adrenal insufficiency.

In severe situations, an increase in dose is immediately required and oral administration of hydrocortisone must be replaced with parenteral treatment. Parenteral administration of hydrocortisone is warranted during transient illness episodes such as severe infections, in particular gastroenteritis associated with vomiting and/or diarrhoea, high fever of any aetiology or extensive physical stress, such as for instance serious accidents and surgery under general anaesthesia, see section 4.4.

In less severe situations when parenteral administration of hydrocortisone is not required, for instance low grade infections, fever of any aetiology and stressful situations such as minor surgical procedures, the normal oral daily replacement dose must be increased temporarily; the PLENADREN total daily dose should be increased by administering the maintenance dose twice or thrice daily with 8 ± 2 hours intervals (an increase in number of administrations, not increasing the morning dose). This regimen has been documented in over 300 intercurrent illness episodes within the clinical study programme. At the discretion of the treating physician, immediate release hydrocortisone tablets can be given instead of PLENADREN or may be added to PLENADREN. Increasing the dose of hydrocortisone at one dose occasion increases the total plasma exposure of cortisol less than proportional, see section 5.2. Once the intercurrent illness episode is over, patients can return to the normal maintenance dose of PLENADREN.

For special populations and the method of administration, refer to the SPC.

05 THERAPEUTIC NEED

Adrenal insufficiency is a disease characterised by a deficit in hormone production by the adrenal glands (glucocorticoids, mineralocorticoids and sex hormones); it can be:

- **primary** (or peripheral) when it is related to a disease of the adrenal glands themselves (e.g.: Addison's disease).
- **secondary** (or central) when linked to impairment of the hypothalamic-pituitary axis resulting in a deficit in ACTH (adrenocorticotropic insufficiency). This impairment may be due to abrupt discontinuation of prolonged corticosteroid therapy, pituitary tumours, infections, trauma, etc.

There are more than 20 different disease that cause adrenal insufficiency; each of them has particular features according to the cause, the hormone deficit and the age of onset. The main complication of this disease is acute adrenal insufficiency.

The management of chronic adrenal insufficiency is based on:
- treating the cause, if applicable,
- hydrocortisone replacement therapy,
- therapeutic education of patients (moderate sodium diet, lifetime treatment, dose adjustment according to general condition, recognising the signs of acute adrenal insufficiency, etc.),
- regular clinical and biological monitoring.

Replacement treatment uses:
- hydrocortisone (HYDROCORTISONE ROUSSEL 10 mg, scored tablet) to correct glucocorticoid deficiencies (20 to 30 mg per day);
- fludrocortisone (ADIXONE 50 µg, tablet) to correct mineralocorticoid deficiencies when they are established (50 to 150 µg per day).
06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

These are all replacement treatments used in the treatment of chronic adrenal insufficiency.

<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Same TC* Yes/No</th>
<th>Indication</th>
<th>Date of opinion AB/IAB (Wording)</th>
<th>Reimbursement Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDROCORTISONE ROUSSEL 10 mg, tablet (hydrocortisone) Sanofi-Aventis France</td>
<td>Yes Glucocorticoid</td>
<td>- Replacement glucocorticoid therapy in adrenal insufficiency: • primary adrenal insufficiency: Addison's disease, adrenalectomy, • adrenal insufficiency of pituitary origin: Sheehan's syndrome, pituitary insufficiency of various causes, • congenital hyperplasia of the adrenals with or without symptoms of loss of salt (Debré-Fibiger syndrome [severe congenital hyperplasia])</td>
<td>Marketing Authorisation 27/04/1995 Renewal of inclusion: 16/10/2013 Substantial AB</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*TC: *therapeutic category

Glucocorticoids (HYDROCORTISONE LEURQUIN, BIOCODEX, ROUSSEL, UPJOHN) and mineralocorticoids (SYNCORTIL) administered by injection, are used in the emergency treatment of acute adrenal insufficiency.

06.2 Other health technologies

Not applicable.

➡️ Conclusion

The clinically relevant comparator is HYDROCORTISONE ROUSSEL 10 mg, tablet.
07  INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSEMENT</th>
<th>Population(s) That of the Marketing Authorisation or restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>General reimbursement</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Yes</td>
<td>General reimbursement</td>
</tr>
<tr>
<td>Denmark</td>
<td>Yes</td>
<td>Individual reimbursement**</td>
</tr>
<tr>
<td>Norway</td>
<td>Yes</td>
<td>Individual reimbursement</td>
</tr>
<tr>
<td>Iceland</td>
<td>Yes</td>
<td>General reimbursement</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>General reimbursement</td>
</tr>
<tr>
<td>Sweden</td>
<td>Yes</td>
<td>Individual reimbursement</td>
</tr>
<tr>
<td>Spain</td>
<td>In progress</td>
<td></td>
</tr>
</tbody>
</table>

*To all patients
**To some patients

The PLENADREN dossier has not been submitted to the FDA.

08  ANALYSIS OF AVAILABLE DATA

The efficacy and safety assessment of PLENADREN in replacement glucocorticoid therapy of adrenal insufficiency is based on:
- a phase II/III clinical study (DC 06/02A) whose objective was to compare PLENADREN (modified-release hydrocortisone) with HYDROCORTISONE ROUSSEL (hydrocortisone LI) in terms of bioavailability and its open-label phase (DC 06/02B) whose objective was to evaluate safety,
- a six-month open-label follow-up of the above-mentioned study (study DC 06/02B),
- another open-label follow-up that included 55 patients from study DC 06/02B and 16 additional patients, (study DC 08/01) whose objective was to determine PLENADREN safety on average over 5 years and for which only the 18-month interim results are available.

08.1  Efficacy: Study DC 06/02A

Method: phase II/III comparative, randomised, open-label crossover study of PLENADREN in a once daily dose (OD3) versus hydrocortisone LI in three doses a day (TID4), carried out in 63 patients followed for two periods of 12 weeks. An open-label 6-month follow-up was also planned (study EC 06/02B).

Inclusion criteria: adult patients with primary adrenal insufficiency, confirmed for more than 6 months and on replacement treatment by TID daily doses of 20, 25, 30 or 40 mg stable for at least 3 months.

Treatment (1:1 randomisation):
PLENADREN once daily at 8:00 (OD)
HYDROCORTISONE ROUSSEL three times a day at 8:00, 12:00 and 16:00 (TID).
The total daily dose of hydrocortisone was identical in both treatment groups and comprised between 20 and 40 mg/day.

2 Patients prescreened for the randomised phase but not included.
3 Once Daily
4 Three times a day
The treatment periods were 12 weeks each.

**Primary efficacy endpoint**: difference in serum cortisol concentration determined by the \( \text{AUC}_{0-24 \text{ h}} \) (area under the curve over 24 h).

Among the secondary endpoints, follow-up of other pharmacokinetic, safety, and quality of life parameters (SF 36, PGWB, VAS scale) and criteria for patient acceptance of the treatment was planned. No evaluation of potential recourse to rescue corticosteroid treatments was planned. Blood pressure monitoring was also planned. Given the methodology of this study, open-label, relying on the dual hypothesis of a reduction of exposure to cortisol and a reduction of the AUC, no conclusion could be drawn from these data. Therefore, they will not be presented in this opinion.

**RESULTS**: ITT analysis (see Table 1).

On inclusion, the patients’ characteristics were as follows:
- mean age: age 47 [19; 71],
- mean weight: 80 kg [54; 121],
- mean BMI: 26.2 kg/m\(^2\) [18.6 ; 37.3],
- Diastolic BP: 124 mmHg [74; 183], Systolic BP: 74 mmHg [48; 105].

Replacement treatment doses were distributed as follows: 20 mg (12.7%), 25 mg (9.5%), 30 mg (58.7%) or 40 mg (19.0%) per day.

**Table 1: results in terms of AUC\(0-24\) (nmol/l) (Primary efficacy endpoint)**

<table>
<thead>
<tr>
<th></th>
<th>PLENADREN (OD)</th>
<th>HYDROCORTISONE ROUSSEL (TID)</th>
<th>Difference</th>
<th>Adjusted quotient over the period p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC 0-24 nmol/l Mean (SD)</td>
<td>3962 (1079.6)</td>
<td>4879.6 (1194.4)</td>
<td>-917.6 (1114.5)</td>
<td>0.806 (0.753-0.862) p &lt; 0.001</td>
</tr>
<tr>
<td>Median [95% CI]</td>
<td>4839.2 (274.2; 7621.4)</td>
<td>-935.2; (-3936.7; 1632.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean AUC 0-24 values were significantly lower with PLENADREN in a once daily dose compared with hydrocortisone three times a day: 3962 nmol/l (1079.6) versus 4879.6 (1194.4), difference -917.6 nmol/l (1114.5), p<0.001. The AUC\(0-24\) was reduced by 19.4% (quotient adjusted to the period: 0.806 [0.753-0.862]); the total exposure to cortisol and its metabolites was therefore lower, but how much the exposure to cortisol alone was reduced could not be established.

There are no data to conclude the clinical consequences of this reduced exposure observed with modified-release hydrocortisone (PLENADREN).

**08.2 Adverse effects**

**08.2.1. Data from clinical studies**

**Study DC 06/02A**

In study DC 06/02A, 38 adverse events were observed in 27/64 patients (35.9%) of the OD group and 12 events were observed in 11/64 (17.2%) patients of the OD group. The most common adverse events were:
- asthenia: seven patients of the OD group versus two of the TID group.
- nausea: three versus one,
- vertigo: one versus two.

These adverse events were more commonly reported in the first 8 weeks of PLENADREN treatment.

**Study DC 06/02B**
Study DC 06/02B is a noncomparative follow-up study of the patients from study DC 06/02A (n=63).
In this study, safety was overall the same as that observed in the randomised phase in 56.6% of patients: unchanged in 73.2% of patients, improved in 10.7% and worsened in 16.1% (p=0.61).

**Study DC 08/01**
This long-term follow-up study included patients who completed study DC 06/02 (n=55) to which new patients were added (n=16).

The (non-hierarchical) endpoints were:
- safety,
- quality of life,
- treatment acceptability.

Only interim results at the 18-month follow-up are available over the planned 5 years on average.

After 18 months, safety was judged compared with the first part of the study:
- unchanged in 67.2% of patients,
- improved in 20.3%,
- worsened in 12.5%.

**08.2.2. SPC data**

According to the SPC: "Overall, 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 to moderate, transient, of short duration but may require dose adjustment or additional concomitant medicinal products. Fatigue has been reported as very common."
Assessment of the efficacy and safety of PLENADREN in replacement therapy of adrenal insufficiency is based on:

- a phase II/III clinical study (DC 0602A) whose objective was to compare PLENADREN (modified-release hydrocortisone) with HYDROCORTISONE ROUSSEL (hydrocortisone LI) in terms of bioavailability and its open-label phase (DC 06/02B) whose objective was to evaluate safety,
- a six-month open-label follow-up of the above-mentioned study (study DC 06/02B),
- another open-label follow-up that included 55 patients from study DC 06/02B and 16 additional patients, (study DC 08/01) whose objective was to determine PLENADREN safety on average over 5 years and for which only the 18-month interim results are available.

**Main efficacy results**
The efficacy data are based on a kinetics study (DC 06/02A) whose objective was to evaluate the bioavailability of PLENADREN (once daily hydrocortisone) versus hydrocortisone in three daily doses.

After 12 weeks of treatment, the mean AUC\textsubscript{0-24} values were significantly lower with PLENADREN in a once daily dose compared with hydrocortisone three times a day: 3962 nmol/l (1079.6) versus 4879.6 (1194.4), difference -917.6 nmol/l (1114.5), p<0.001. The AUC\textsubscript{0-24} was reduced by 19.4% (quotient adjusted to the period: 0.806 [0.753-0.862]); the total exposure to cortisol and its metabolites was therefore lower, but how much the exposure to cortisol alone was reduced could not be established.

There are no data to conclude the clinical consequences of this reduced exposure observed with modified-release hydrocortisone (PLENADREN).

**Main safety results**
In study DC 06/02A, 38 adverse events were observed in 27/64 patients (35.9%) treated in a once daily dose (PLENADREN) and 12 events were observed in 11/64 (17.2%) patients.

The most common adverse events were asthenia, nausea and vertigo.

The frequency and type of adverse effects were similar for PLENADREN once daily modified-release tablets and hydrocortisone tablets given three times daily. There was an initial increase in the frequency of adverse effects 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. These adverse effects (abdominal pain, diarrhoea, nausea and fatigue) are mild to moderate, transient, of short duration but may require dose adjustment or additional concomitant medicinal products.

**Discussion:**
The data rely on a pharmacokinetic study that does not permit conclusions on the clinical consequences of the reduced total exposure to cortisol and its metabolites to be drawn.

Furthermore, in this study, only patients with primary adrenal insufficiency were included; there are no data for patients with secondary adrenal insufficiency.

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\textsuperscript{5} Patients prescreened for the randomised phase but not included.
08.4 Planned studies

The EMA has validated the Marketing Authorisation for PLENADREN by requiring the company to conduct studies to improve the assessment of the efficacy and safety of PLENADREN under actual conditions of use:

- Patients under and overdosed with glucocorticoids: The EU-AIR registry (European, prospective, multicentre) concerning chronic adrenal insufficiency;
- Off-label use in adults and children and pregnant women: EU-AIR and SWE-DUS registries (retrospective Swedish registries).

As part of the RMP, studies are also underway in special patient populations: patients under and overdosed with glucocorticoids, off-label use in adults and children and in pregnant women.

09 THERAPEUTIC USE

Adrenal insufficiency is a disease characterised by a deficit in hormone production by the adrenal glands (glucocorticoids, mineralocorticoids and sex hormones).

Replacement treatment consists of the administration of hydrocortisone (HYDROCORTISONE ROUSSEL 10 mg, scored tablet) 20 to 30 mg per day, reference treatment, in combination with fludrocortisone (ADIXONE 50 µg, tablet) 50 to 150 mg per day when mineralocorticoid treatment is necessary.

Role of PLENADREN:
PLENADREN is a new proprietary medicinal product based on hydrocortisone administered orally, with a modified-release dosage form that represents an alternative to immediate-release HYDROCORTISONE ROUSSEL.
010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

- Primary or secondary adrenal insufficiency is a serious disease which, in the absence of treatment, leads to a notable reduction in quality of life and can be life-threatening.
- PLENADREN is intended as replacement therapy.
- Its efficacy/adverse effects ratio is high.
- There is a treatment alternative: HYDROCORTISONE ROUSSEL.
- Glucocorticoids are first-line therapies.
  - Public health benefit:
    Adrenal insufficiency in adults and children is a serious condition, which can be life-threatening in the absence of treatment, but is a low public health burden because of its rarity.
    Improving the management of adrenal insufficiency patients is a public health need which is an established priority (GTNDO [National Technical Group for Definition of Public Health Objectives]<574></574,* Plan for Rare Diseases, Plan for improving quality of life in patients with chronic diseases).
    Despite its new modified-release dosage form and given the existence of a proprietary medicinal product based on oral hydrocortisone, there is no expected additional impact in terms of morbidity and mortality (acute adrenal insufficiency episodes) and quality of life for PLENADREN.
    PLENADREN is not likely to provide an additional response to the public health need identified and will not change patient access to care.
    It is not expected therefore that this proprietary medicinal product will benefit public health.

Consequently, the Committee considers that the actual benefit of PLENADREN is substantial in the Marketing Authorisation indication.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the indication "Treatment of adrenal insufficiency in adults" and at the dosages in the Marketing Authorisation.

- Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

The PLENADREN modified-release dosage form of hydrocortisone is closer to the pharmacokinetic profile of the physiological rhythm of cortisol, without any clinical consequence being demonstrated. Consequently, PLENADREN provides a minor improvement in actual benefit (IAB IV) in the care of patients with adrenal insufficiency.
010.3  Target population

The target population of PLENADREN is patients with adrenal insufficiency. According to the data in the EPAR, the prevalence of adrenal insufficiency may be estimated at 4.5/10,000 people, which, relative to the adult French population, permits the target population to be estimated at 22,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

- **Packaging:**
  Packaging is not adjusted to the prescribing conditions as regards the indication, dosage and treatment duration. The Committee wishes to reiterate that, in accordance with its deliberations of 20 July 2005, it recommends the standardisation of pack sizes for treatments lasting one month to the equivalent of 30 days of treatment.