**TRANSPARENCY COMMITTEE**  
Opinion  
17 September 2014

**ALPRESS LP 2.5 mg, prolonged-release osmotic tablet**  
B/30 (CIP: 331 177-5)  
B/90 (CIP: 372 965-8)

**ALPRESS LP 5 mg, prolonged-release osmotic tablet**  
B/30 tablets (CIP: 331 172-3)  
B/90 tablets (CIP: 372 966-4)

Applicant: PFIZER

<table>
<thead>
<tr>
<th>INN</th>
<th>Prazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2011)</td>
<td>C02CA01 (peripherally acting adrenolytic antihypertensive/alpha blockers)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Re-assessment of the actual benefit at the request of the Committee, in accordance with article R 163-21 of the French Social Security Code.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lists concerned</th>
<th></th>
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<tbody>
<tr>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
<td></td>
</tr>
<tr>
<td>Hospital use (French Public Health Code L.5123-2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication concerned</th>
<th>&quot;Hypertension.&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Benefit</td>
<td>The actual benefit of ALPRESS remains substantial in the treatment of hypertension</td>
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<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Therapeutic Use</td>
<td>Since alpha-blockers, including ALPRESS (prolonged-release prazosin), have not demonstrated their efficacy in terms of morbidity-mortality, they are only recommended as a last-resort treatment for rare patients experiencing adverse effects during treatment with one of the five classes of antihypertensive treatments having demonstrated their efficacy on morbidity and mortality or from the triple therapy stage to help reach the unachieved blood pressure target.</td>
</tr>
<tr>
<td>Recommendations</td>
<td>The Transparency Committee recommends continued inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals.</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th>Marketing Authorisation (procedure)</th>
<th>Initial date (national); ALPRESS: 22 June 1988</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing and dispensing conditions/special status</td>
<td>List I</td>
</tr>
</tbody>
</table>
| ATC Classification | 2011 Cardiovascular system  
|                    | C02 Antihypertensives  
|                    | C02C Antiadrenergic agents, peripherally acting  
|                    | C02CA Alpha-adrenoreceptor antagonists  
|                    | C02CA01 prazosin |

02 BACKGROUND

In its opinion on the request for renewal of inclusion of MINIPRESS (immediate-release prazosin) on 30 April 2008, the Transparency Committee deemed that its actual benefit was insufficient; this conclusion was confirmed in the opinion on deletion from the list of medicines reimbursed by National Insurance following the joint request from the Ministry of Health and the social security Directorate, in accordance with articles R.163-19/6° and R.163-7 of the French Social Security Code on 22 June 2011.

On 7 May 2012, the Social Security Directorate and the Ministry of Health jointly instructed the Transparency Committee to re-assess the actual benefit of the proprietary medicinal products ALPRESS LP 2.5 and 5 mg. An opinion for ALPRESS (prolonged-release prazosin) on 18 July 2012 was made and the Transparency Committee considered that its AB remained substantial.

On 3 December 2012, the Ministry of Social Affairs and Health informed Laphal, MINIPRESS distributor, of its intention to delete this proprietary medicinal product from the list of medicines reimbursed by National Insurance; the company challenged the validity of this deletion based on the opinion given to their competitor, ALPRESS.

In this context, and in the interest of fairness, the Committee wished to jointly re-assess the AB of the prazosin-based proprietary medicinal products, ALPRESS and MINIPRESS, in the "hypertension" indication, subject of this opinion.

03 THERAPEUTIC INDICATION

"Hypertension"

04 DOSAGE

See SPC.
In uncomplicated essential hypertension, some thiazide diuretics, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers demonstrated a benefit in clinical trials in the prevention of cardiovascular events and death from any cause. The medicines in these classes are therefore recommended for first-line use in the management of patients with uncomplicated essential hypertension.

In most hypertensive patients, therapeutic needs are met by using these five classes of antihypertensives.

In patients who are not controlled by medicines in these five classes, used alone or in combination, other classes of antihypertensive that have shown efficacy only in the reduction of blood pressure can be used: vasodilators, alpha-blockers, central antihypertensives.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Prazosin (ALPRESS) is a representative of the alpha-blocker class, alongside urapidil (EUPRESSYL). The other comparators are the other antihypertensive medicinal products that have shown efficacy only in the reduction of blood pressure and used as a last-resort.

<table>
<thead>
<tr>
<th>NAME (INN)</th>
<th>Same TC* Yes/No</th>
<th>Indication</th>
<th>Date of opinion</th>
<th>AB/AB (Wording)</th>
<th>Reimbursement Yes/No</th>
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</thead>
<tbody>
<tr>
<td>MINIPRESS (immediate-release prazosin)</td>
<td>Yes</td>
<td>Hypertension</td>
<td>22/06/2011</td>
<td>Insufficient Actual Benefit</td>
<td>No</td>
</tr>
<tr>
<td>EUPRESSYL MEDIATENSYL (urapidil) Takeda</td>
<td>Yes</td>
<td>Hypertension</td>
<td>05/09/2012</td>
<td>Substantial AB starting from the triple therapy stage</td>
<td>Yes</td>
</tr>
<tr>
<td>ALDOMET (methyldopa) Iroko Products Ld</td>
<td>No</td>
<td>Moderate to severe hypertension</td>
<td>06/03/2012</td>
<td>Substantial AB starting from the triple therapy stage</td>
<td>Yes</td>
</tr>
<tr>
<td>CATAPRESSAN (clonidine) Boehringer Ingelheim</td>
<td>No</td>
<td>Hypertension</td>
<td>04/09/2012</td>
<td>Substantial AB starting from the triple therapy stage</td>
<td>Yes</td>
</tr>
<tr>
<td>HYPERIUM (rilmenidine) Servier</td>
<td>No</td>
<td>Hypertension</td>
<td>09/03/2011</td>
<td>Moderate AB</td>
<td>Yes</td>
</tr>
<tr>
<td>PHYSIOTENS (moxonidine) Abbott</td>
<td>No</td>
<td></td>
<td>09/03/2011</td>
<td>moderate AB</td>
<td>Yes</td>
</tr>
<tr>
<td>TENSIONORME (bendroflumethiazide, reserpine) Lisa-Pharm</td>
<td>No</td>
<td>Hypertension</td>
<td>05/03/2014</td>
<td>Substantial AB starting from the triple therapy stage</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*therapeutic category

**Conclusion**

The comparators listed are all clinically relevant.
## SUMMARY OF PREVIOUS ASSESSMENTS

| Date of opinion (reason for the review) | 18 July 2012  
Renewal of inclusion  
| Indication | Hypertension |
| AB (wording) | Substantial |
| Therapeutic Use | Alpha-blockers must only be used after considering all the therapeutic alternatives that have demonstrated their efficacy on cardiovascular morbidity and mortality. In this context, alpha-blockers can be used in combination in certain insufficiently controlled patients |
08 DATA

ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

8.1.1 ALPRESS studies

The company has reported nine clinical studies (see table in the appendix):
- Five randomised clinical studies:
  - Two versus active comparators (enalapril in the Luccioni study in 1996\(^4\) and nicardipine in the Galinier study in 1990\(^5\)) which demonstrate no difference in terms of blood pressure reduction between the studied medicinal products,
  - one versus placebo (Singleton, 1989)\(^6\) which revealed a greater blood pressure reduction with prazosin versus placebo in 205 patients with mild to moderate hypertension.
  - one study versus MINIPRESS (Escande, 1996)\(^7\) which will be detailed in paragraph 8.1.3.
  - one study with the objective of comparing the benefit of prazosin in terms of quality of life (evaluated by 22 items) compared with ACE inhibitors in 100 hypertensive patients treated for 24 weeks (Consoli, 2000)\(^8\) which revealed an improvement of the studied quality of life elements in the prazosin group.
- three uncontrolled studies evaluating the efficacy of prazosin on blood pressure (before/after studies) which tended to demonstrate a reduction in blood pressure after treatment compared with baseline:
  - one open-label study: Hanon 2000\(^9\)
  - two real-life studies: Haiat, 1996\(^10\) and Neimann, 1989\(^11\)

Given the methodological weaknesses of these studies (old studies, performed in patients in whom the management does not comply with current recommendations, low numbers, no comparator arm, descriptive analysis, short duration of follow-up etc.), the results must be interpreted with caution.

These studies appear to confirm the efficacy of prazosin in terms of reducing blood pressure compared with a placebo even if the observed effect is low.

8.1.2 ALPRESS versus MINIPRESS comparative study

The 1996 comparative, randomised, double-blind, Escande study\(^7\) compared the efficacy and safety of prolonged-release prazosin (ALPRESS) with immediate-release prazosin (MINIPRESS).\(^4\) Luccioni et al. A randomised comparison of prazosin GITS and enalapril in mild to moderate hypertension. Indian Heart J 1196; 48: 37-40.
in terms of blood pressure reduction and potential impact on heart rate in 23 elderly patients (> 65 years) with mild to moderate essential hypertension (95<diastolic BP<115 mmHg) with a 2-week follow-up.

The primary efficacy endpoint was reduction of blood pressure; the subjects were considered to have returned to normal with diastolic BP<90 mmHg.

Treatments:
- 0.5 mg immediate-release prazosin + 2.5 mg prolonged-release prazosin then 0.5 mg prolonged-release prazosin + 0.5 mg immediate-release prazosin
- 0.5 mg prolonged-release prazosin + 2.5 mg immediate-release prazosin then 0.5 mg immediate-release prazosin + 0.5 mg prolonged-release prazosin

After 2 weeks, no difference was observed in terms of BP reduction or response rate between the two studied groups (statistical test not available). Variations in terms of heart rate were observed: 0.1 ± 0.2 bpm in the prolonged-release group versus 2.1 ± 2.2 bpm in the immediate-release group, statistical test not available.

Given the methodological weaknesses of this study (old studies, performed in patients in whom the management does not comply with current recommendations, low numbers, descriptive analysis, short duration of follow-up etc.), the results must be interpreted with caution.

08.2 Adverse Effects

8.2.1 PSUR data

The analysis of the last periodic safety update reports (PSUR) covering the period from 1 April 2009 to 13 March 2012 enables the exposure of patients to the treatment in France to be estimated at 195,942 patient-years. During this period, 18 French cases comprising 53 events were reported. Analysis of this data did not reveal any safety information likely to change the benefit/risk ratio of this product.

In the last 5 years, the data from the literature and the pharmacovigilance summaries did not reveal any new safety information likely to change the benefit/risk ratio of ALPRESS.

8.2.2 SPC data

According to the SPC, the following adverse effects can occur and must be carefully monitored: "asthenia, malaise, sweating, orthostatic hypotension, exceptionally with loss of consciousness, angina pectoris, hypotension, syncope, bradycardia, tachycardia, oedema of the legs, facial flushing, allergic reactions, allergic-type skin rash (pruritus, urticaria), vertigo, headaches, tinnitus, drowsiness, insomnia, blurred vision, paraesthesia, worsening of pre-existing narcolepsy (Gelineau syndrome) associated with prazosin treatment has been described in the literature, nausea, vomiting, constipation, diarrhoea, epigastric pain, dry mouth, nasal or ocular congestion, epistaxis, priapism, pollakiuria, urinary incontinence, impotence, gynaecomastia, joint pain".
08.3 Prescription data

According to the IMS-EPPM [permanent survey of medical prescription] data (moving annual total, autumn 2013), 171,000 prescriptions were written for ALPRESS. ALPRESS is mainly prescribed for hypertension (77.7 to 87.7% of prescriptions depending on the pharmaceutical form and dosages).

08.4 Summary and discussion

Primary efficacy data
The clinical data enabling the efficacy of prolonged-release prazosin to be evaluated in terms of blood pressure reduction is based on studies comprising numerous methodological weaknesses (old studies, performed in patients for whom the management does not comply with current recommendations, low numbers, no comparator arm, descriptive analysis, short duration of follow-up etc.). Therefore, their results must be interpreted with caution. Nevertheless, these studies appear to confirm the efficacy of prolonged-release prazosin in terms of reducing blood pressure compared with a placebo even though the observed effect is low.

Primary safety data
The analysis of the last PSURs did not reveal any poor safety data for prolonged-release prazosin.

Discussion
The efficacy of prolonged-release prazosin in patients with mild to moderate essential hypertension has only been demonstrated on an intermediate endpoint, the reduction of blood pressure. No study with an objective of demonstrating the efficacy of prolonged-release prazosin in terms of morbidity-mortality is currently available.

Even though the pharmacokinetic profiles of ALPRESS (prolonged-release prazosin) and MINIPRESS (immediate-release prazosin) are different, we do not have clinical studies enabling the two dosage forms to be differentiated in terms of efficacy on blood pressure.

08.5 Planned studies

The company has not reported any studies, either in progress or to come.
Diet and lifestyle measures are recommended for all hypertensive patients regardless of their blood pressure, with or without associated drug treatment.

In uncomplicated essential hypertension, some thiazide diuretics, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers showed a benefit in the prevention of cardiovascular events and death from any cause. The medicines in these classes are therefore recommended for first-line use in the management of patients with uncomplicated essential hypertension.

In most hypertensive patients, therapeutic needs are met by using these five classes of antihypertensives. In patients who are not controlled by the medicines in these five classes, used alone or in combination, other classes of antihypertensives that have shown efficacy only in the reduction of blood pressure can be used: vasodilators, alpha-blockers, central antihypertensives.

**Role of ALPRESS:**
Since alpha-blockers, including ALPRESS (prolonged-release prazosin), have not demonstrated their efficacy in terms of morbidity-mortality, they are only recommended as a last-resort treatment for rare patients experiencing adverse effects during treatment with one of the five classes of antihypertensive treatments having demonstrated their efficacy on morbidity and mortality, or from the triple therapy stage to help reach the unachieved blood pressure target.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

- Essential hypertension, due to its complications, can be life-threatening.
- These proprietary medicinal products are intended as preventive therapy.
- In the majority of hypertensive patients, the therapeutic needs are covered by use of the five classes of antihypertensives (diuretics, ACE inhibitors, ARBs, calcium-channel blockers and beta-blockers), most of the active substances of which have demonstrated an efficacy on morbidity and mortality in the prevention of cardiovascular events and death from any cause.
- Given the demonstrated efficacy only in terms of blood pressure reduction and the safety profile, the efficacy/adverse effects ratio of ALPRESS is substantial.
- Prolonged-release prazosin (ALPRESS) is an antihypertensive which must be kept as a last-resort treatment for patients not controlled by any of the five classes of antihypertensives (alone or in combination) having demonstrated their efficacy in terms of morbidity-mortality. In this context, it must be reserved for rare patients if adverse effects occur or from the triple therapy stage to help reach the unachieved blood pressure target.

Consequently, the Committee considers that the actual benefit of ALPRESS remains substantial in the "hypertension" indication.

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the "hypertension" indication and at the dosages in the Marketing Authorisation in rare patients if adverse effects occur or from the triple therapy stage to help reach the unachieved blood pressure target.

- Proposed reimbursement rate: 65%

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

- Packaging
  Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.
# Appendix

## Summary of clinical studies: ALPRESS (prolonged-release prazosin)

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Study population</th>
<th>Results</th>
</tr>
</thead>
</table>
| **Luccioni 1996** | Controlled, randomised clinical study of prazosin GITS 2.5 to 10 mg/day versus enalapril 10 to 40 mg/day. Follow-up: 12 weeks. 3 non-ranked endpoints | N=78 Patients with uncomplicated mild to moderate hypertension (96<diastolic BP<114 mmHg) | Reduction of blood pressure between the start and the end of the study  
Prazosin GITS: reduction from 180.7/104.5 mmHg to 146/82.6 mmHg,  
Enalapril: reduction from 172/102 mmHg to 149/82.6 mmHg.  
Descriptive analysis  
Number of patients with normalised blood pressure  
Prazosin GITS: 78.4% CI (61.8-90.2%)  
Enalapril: 60.6% CI (42.1-77.1%)  
Difference: NS  
Response rate  
Prazosin GITS: 100% CI (90.5-100%)  
Enalapril: 87.9% CI (71.8-96.6%)  
p=0.045 | |
| **Galinier 1990** | Controlled, randomised, open-label clinical study of prolonged-release prazosin 2.5 to 10 mg/day versus prolonged-release nicardipine 50 mg x2/day. Follow-up: 12 weeks. 2 non-ranked endpoints | N=83 Patients with uncomplicated essential hypertension (90<diastolic BP<115 mmHg) | Reduction of the systolic and diastolic blood pressure values  
Diastolic BP  
Prolonged-release prazosin: reduction from 103 to 84 mmHg  
Nicardipine: from 102 to 85 mmHg  
Difference: NS  
Systolic blood pressure  
Prolonged-release prazosin: reduction from 174 to 147 mmHg  
Nicardipine: reduction from 180 to 154 mmHg  
Difference: NS  
Normalisation of blood pressure  
Prazosin: 75% of patients  
Nicardipine: 55% of patients  
p=0.0389 | |
| **Singletor 1989** | Double-blind, randomised clinical study of, prolonged-release prazosin 2.5 to 20 mg/day versus placebo. A diuretic was added in patients with moderate hypertension. Follow-up: 8 weeks.  
Endpoint: change in BP | N=205 Patients with mild to moderate essential hypertension (95<diastolic BP<105 mmHg). | As monotherapy  
Prolonged-release prazosin 10 mg: -11.5/-10.7 mmHg,  
Prolonged-release prazosin 20 mg: -14.0/-10.9 mmHg,  
Placebo: -2.3/-3.9 mmHg,  
p=0.01  
Prazosin GITS + diuretic combination  
Prolonged-release prazosin 10 mg: -10.6/-9.4 mmHg  
Prolonged-release prazosin 20 mg: -12.1/-10.3 mmHg,  
Placebo: -4.6/-7.2 mmHg,  
p=0.05 except for prazosin 10 mg versus placebo diastolic BP: NS |
<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Design</th>
<th>Endpoint</th>
<th>Follow-up</th>
<th>N</th>
<th>Efficacy on quality of life</th>
<th>Efficacy on blood pressure</th>
<th>Normalisation of blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consoli 2000</td>
<td>Double-blind, randomised clinical study of prolonged-release prazosin 2.5 versus enalapril 10 mg Follow-up: 24 weeks</td>
<td></td>
<td>Quality of life evaluated with a self-administered QVH-22 questionnaire based on 22 items (rating from 0=minimum to 66=excellent)</td>
<td>24 weeks</td>
<td>104</td>
<td>Patients with mild to moderate hypertension (96&lt;diastolic BP&lt;114 mmHg)</td>
<td>Reduction of the overall score calculated for the entire population of 47.1 +/- 8.9 to 53.4 +/- 8.3 after 24 weeks of treatment. p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hanon 2000</td>
<td>Uncontrolled clinical study of prolonged-release prazosin 2.5 to 5 mg/day. Follow-up: 12 weeks</td>
<td></td>
<td>change in BP</td>
<td>12 weeks</td>
<td>74</td>
<td>Insulin dependent diabetic patients with mild to moderate hypertension (90&lt;diastolic BP&lt;115 mmHg, 140&lt;systolic BP&lt;180 mmHg)</td>
<td>Systolic BP: reduction of -13 +/- 14 mmHg in a lying position and -12 +/- 14 mmHg in a standing position (p&lt;0.001) Diastolic BP: reduction of -11 +/- 9 mmHg in a lying position and -10 +/- 9 mmHg in a standing position (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Haiat 1996</td>
<td>Uncontrolled real-life observational study Prazosin GITS 2.5 to 10 mg/day Follow-up: 6 weeks</td>
<td></td>
<td>change in BP and rate of normalised patients (systolic BP&lt;160 mmHg, diastolic BP&lt;90 mmHg)</td>
<td>6 weeks</td>
<td>74</td>
<td>Patients with mild to moderate hypertension (95&lt;diastolic BP&lt;114 mmHg)</td>
<td>Systolic blood pressure: reduced from 174 +/- 14 to 150 +/- 12 Diastolic blood pressure: reduced from 103 +/- 6 mmHg to 86 +/- 7</td>
<td>89% of patients with normalised diastolic BP and 73% of patients with normalised systolic and diastolic BP</td>
</tr>
<tr>
<td>Neimann 1989</td>
<td>Uncontrolled real-life observational study Prolonged-release prazosin Follow-up: 12 weeks</td>
<td></td>
<td>rate of normalised patients (diastolic BP reduction&gt;10 mmHg)</td>
<td>12 weeks</td>
<td>50</td>
<td>Patients with mild to moderate hypertension (80&lt;diastolic BP&lt;120 mmHg)</td>
<td>93% of patients with normalised diastolic BP and 88% of patients with normalised systolic and diastolic BP</td>
<td></td>
</tr>
</tbody>
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