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TRANSPARENCY COMMITTEE

Opinion
17 September 2014

MINIPRESS 1 mg, scored tablet

B/30 (CIP: 322 470-5)

B/90 (CIP: 372 962-9)

MINIPRESS 5 mg, scored tablet

B/30 (CIP: 322 471-1)

B/90 (CIP: 372 961-2)

Applicant: LAPHAL Industries

INN	Immediate-release prazosin
ATC Code (2011)	C02CA01 (peripherally acting adrenolytic antihypertensive/alpha-blockers)
Reason for the review	Re-assessment at the request of the Committee, in accordance with article R 163-21 of the French Social Security Code.
Lists concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)
Indication concerned	"Hypertension. "

Actual Benefit	The actual benefit of MINIPRESS (immediate-release prazosin) remains insufficient in the treatment of arterial hypertension.
Improvement in Actual Benefit	Not applicable
Therapeutic use	Not applicable

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (national); MINIPRESS: 8 April 1981	
Prescribing and dispensing conditions/special status	List I	
ATC Classification	2011 C C02 C02C C02CA C02CA01	Cardiovascular system Antihypertensives Antiadrenergic agents, peripherally acting Alpha-adrenoreceptor antagonists 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 Ministry of Health and 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 (PR prazosin) on 18 July 2012 was made and the Transparency Committee considered that its AB was substantial.

On 3 December 2012, the Ministry of Social Affairs and Health informed Laphal Industries, MINIPRESS distributor, of its intention to delete this proprietary medicinal product from the list; the company challenged the validity of this removal 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.

Congestive left-sided heart failure.

NB:

- the efficacy of prazosin in left ventricular heart failure following recent myocardial infarction has not been demonstrated.
- isolated mild or moderate left ventricular heart failure is not an indication of the product.

Symptomatic treatment of Raynaud's phenomenon (primary or secondary).

Symptomatic treatment of certain functional manifestations related to benign prostatic hyperplasia, in particular pollakiuria due to the post-void residual urine and dysuria:

- in cases where surgery must be postponed. However, this treatment must not delay the diagnosis of prostatic obstruction requiring surgical treatment,
- during episodes of adenoma progression when the symptomatology is increased and especially in more elderly patients."

This opinion focuses only on the "hypertension" indication.

The insufficient AB issued for the other indications will not be re assessed.

04 DOSAGE

- "The dosage depends on the indication.
- Tolerability is better if the treatment is initiated at a low dose.
- During the first week, the dosage will be adjusted depending on the individual tolerance of the patient. The dosage will be gradually increased until the effective dose is reached.

Hypertension

Prazosin can be used alone or in combination with a diuretic and/or other antihypertensives.

Treatment of hypertension is started with 1 mg tablets.

The first dose of 0.5 mg will be taken in the evening before going to bed.

Dosage increase depending on the clinical response must be performed in stages, every 2 or 3 days, under close medical monitoring.

The following treatment regimen is normally used in hospital and enables faster dosage increase.

Practical experience in outpatient treatment enables the following regimen to be recommended. It is more easily accepted by the patient and therefore promotes better compliance during the initial treatment phase.

- Initiation phase:

Start the treatment as follows:

		morning	evening before going to bed
1st day	0.5 mg	-	½ tablet, i.e. 0.5 mg
1st week from 2nd to 7th day	1 mg	½ tablet, i.e. 0.5 mg	½ tablet, i.e. 0.5 mg
2nd week	2 mg	1 tablet, i.e. 1 mg	1 tablet, i.e. 1 mg
3rd week	3 mg	1 ½ tablets, i.e. 1.5 mg	1 ½ tablets, i.e. 1.5 mg

Continue the treatment. See the patient again. The decision to increase the dosage again and the modalities of this increase will depend on the obtained results.

Continuation of treatment, according to the individual case, will be with either 1 mg tablets or tablets of 2 mg or 5 mg.

If necessary, continue to increase the dosage to a maximum of 20 mg, in increments of 2 to 2.5 mg per week, depending on the clinical response and the tolerance.

o Prazosin used alone: the effective daily dose is between 2 and 20 mg, most often between 3 and 7.5 mg in two doses. The daily dose can also be taken in three doses.

o If combined with other antihypertensives or hypotensives: the potentiation which could ensue must be taken into account and the dosages reduced accordingly."

05 THERAPEUTIC NEED^{1,2,3}

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.

¹ SFHTA (Société Française d'HyperTension Artérielle). Blacher J et al. Prise en charge de l'hypertension artérielle de l'adulte. *Press Med.* 2013; 42: 819-25.

² ESH (European Society of Hypertension) & ESC (European Society of Cardiology). Mancia G, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J.* 2013; 34: 2159-219.

³ NICE (National Institution for Health and Care Excellence). Hypertension. Clinical management of primary hypertension in adults. NICE Clinical Guideline 34. August 2011.

1 06 CLINICALLY RELEVANT COMPARATORS

2 06.1 Medicinal products

3 Immediate-release prazosin (MINIPRESS) is a representative of the alpha-blocker class, alongside urapidil (EUPRESSYL). The other comparators
4 are the other antihypertensive medicinal products that have shown efficacy only in the reduction of blood pressure and used as a last-resort.
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NAME (INN) <i>Company</i>	Same TC* Yes/No	Indication	Date of opinion	AB/IAB (Wording)	Reimbursement Yes/No
Alpha-blockers					
ALPRESS (prolonged-release prazosin)	Yes	Hypertension	18/07/2012	Substantial AB starting from the triple therapy stage	Yes
EUPRESSYL MEDIATENSYL (urapidil) Takeda	Yes	Hypertension	05/09/2012	Substantial AB starting from the triple therapy stage	Yes
Centrally acting antihypertensives					
ALDOMET (methyldopa) Iroko Products Ld	No	Moderate to severe hypertension	06/03/2012	Substantial AB starting from the triple therapy stage	Yes
CATAPRESSAN (clonidine) Boehringer Ingelheim	No	Hypertension	04/09/2012	Substantial AB starting from the triple therapy stage	Yes
HYPERIUM (rilmenidine) Servier	No		09/03/2011	Moderate AB	Yes
PHYSIOTENS (moxonidine) Abbott	No		09/03/2011	Moderate AB	Yes
Centrally acting antihypertensives in fixed combination					
TENSIONORME (bendroflumethiazide, reserpine) Lisa-Pharm	No	Hypertension	05/03/2014	Substantial AB starting from the triple therapy stage	Yes

6 *therapeutic category

7

8 ► Conclusion

9 The comparators listed are all clinically relevant.

1 07 SUMMARY OF PREVIOUS ASSESSMENTS

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Date of opinion (reason for the review)	1 June 1999 Re-assessment
Indication	Treatment of hypertension regardless of the cause and the degree of severity
Actual Benefit (wording)	moderate

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Date of opinion (reason for the review)	30 April 2008 Renewal of inclusion
Indication	Hypertension
Actual Benefit (wording)	Insufficient

4

Date of opinion (reason for the review)	22 June 2011 Opinion in light of deletion from the list
Indication	Hypertension
Actual Benefit (wording)	Insufficient

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

8.1.1 MINIPRESS studies

A/ Data submitted by the company

The company has reported three randomised clinical studies (see table in the appendix):

- two versus the active comparator, doxazosin, not available in France, in the hypertension indication (Torvik, 1996)⁴ and hydralazine (Vandenburg, 1983)⁵ which revealed an absence of difference in terms of blood pressure reduction between the active arms and a difference compared with the placebo,
- one versus placebo (Materson, 1995)⁶ which revealed a greater blood pressure reduction on prazosin versus placebo in patients with mild to moderate hypertension.

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.

one study compared ALPRESS with MINIPRESS (Escande, 1996)⁷ which will be detailed in paragraph 8.1.2.

The company also mentioned the existence of two studies evaluating the mechanism of action and the kinetics of immediate-release (IR) prazosin (Davey, 1986, Stanaszek, 1983) which will not be discussed in this opinion due to their non-clinical objective. Similarly, the subgroup analysis of the Materson study, 1995, and the Koshy, 1977 and Ajayi, 1996 studies performed on 14 and 12 patients respectively, will not be discussed in this opinion.

B/ Data from the literature: Materson study, 1993⁸ (corrected by the Materson study, 1995)⁶

The objective of this double-blind study was to compare the efficacy and safety of the placebo with six antihypertensive medicinal products used as monotherapy (hydrochlorothiazide 12.5 to 50 mg, atenolol 25 to 100 mg, captopril 25 to 100 mg, clonidine 0.2 to 0.6 mg, PR diltiazem 120 to 360 mg and IR prazosin⁹ 4 to 20 mg) in 1292 adults¹⁰ with mild to moderate hypertension (95<diastolic BP<109 mmHg).

The included patients had a mean age of 59 ± 10 years and a mean BP of 152 ± 14/99 ± 3 mmHg.

⁴ Torvik et al. Multicentre 12-week double-blind comparison of doxazosin, prazosin and placebo in patients with mild to moderate essential hypertension. Br. J. clin. Pharmac 1986; 21: 69S-75S.

⁵ Vandenburg et al. Hydralazine and prazosin in the treatment of hypertension Br J Clin Pharmacol 1983; 16: 537-42.

⁶ Materson et al. Department of Veterans Affairs Single-Drug Therapy of Hypertension Study : Revised Figures and New Data. AJH 1995; 8: 189-92.

⁷ Escande et al. Response to Prazosin GITS Compared with plain Prazosin Tablets in Elderly Hypertensive Patients. Indian Heart J 1996; 48: 27-30.

⁸ Materson et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. NEJM 1993; 328: 914-21.

⁹ When the study was conducted, only the IR form was available. This information was confirmed by the study author, Barry Materson.

¹⁰ From the department of veterans affairs.

The level of success, defined by reaching a target diastolic BP of 90 mmHg (primary efficacy endpoint) was significantly higher in the treated groups compared with the placebo group (p<0.001):

- 72% of patients on diltiazem,
- 62% of patients on atenolol,
- 60% of patients on clonidine,
- 55% of patients on hydrochlorothiazide,
- 54% of patients on prazosin,
- 550% of patients on captopril,
- 31% of patients on placebo,

The authors concluded that there was a significantly greater efficacy of the active treatments compared with the placebo, with diltiazem producing better response maintenance compared with the other treatments.

8.1.2 ALPRESS versus MINIPRESS comparative study

The 1996 comparative, randomised, double-blind, Escande study⁷ compared the efficacy and safety of prolonged-release prazosin (ALPRESS) with immediate-release prazosin (MINIPRESS) 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 company submitted an analysis of the last PSUR covering the period from January 1999 to March 2012 and presented the data relating to hypotension (see table below).

PERIOD COVERED	NUMBER OF CASES REPORTED	CASES RELATING TO HYPOTENSION	RELATIVE INCIDENCE OF HYPOTENSION
01/01/1999 – 13/03/2012	292 cases IR prazosin	21 cases of hypotension	7.19%
		21 cases of orthostatic hypotension	7.19%
	233 cases PR prazosin	25 cases of hypotension	10.73%
		32 cases of orthostatic hypotension	13.73%

Given the low number of observed events and the absence of statistical test, the observed differences between the two forms of prazosin cannot be interpreted.

8.2.2 SPC data

MINIPRESS

According to the SPC, the following adverse effects can occur and must be carefully monitored: "asthenia, malaise, sweating, orthostatic hypotension sometimes with loss of consciousness at the start of treatment of the hypertension (see Special warnings), risk of worsening anxiety in patients not treated with an additional protective treatment, hypotension, syncope, bradycardia, tachycardia, palpitations, sodium retention syndrome with onset of oedema and weight gain, mainly in certain patients with heart failure, facial flushing, allergic type skin rashes (such as pruritus, urticaria), headaches, tinnitus, drowsiness, insomnia, visual impairment, paraesthesia, nausea, constipation, diarrhoea, dry mouth, epistaxis, conjunctival hyperaemia, epiphora, nasal congestion, priapism, pollakiuria, urinary incontinence, impotence, gynaecomastia, joint pain, positive ANA titre"

8.2.3 From literature data: Materson, 19938

In this double-blind study, the objective of which was to compare the efficacy and safety of a placebo with six antihypertensive medicines used as monotherapy, performed on 1200 patients with mild to moderate arterial hypertension, the adverse effects were most commonly encountered in the groups treated with clonidine (14%) and IR prazosin (MINIPRESS) (12%).

The most commonly observed adverse events (> 10%) were:

- Fatigue: 13% on clonidine, 13% on IR prazosin and 8% on placebo,
- Drowsiness: 30% vs. 12% vs. 6%,
- Hypotension: 8% versus 12% versus 5%.

Hypotension was observed in 12% of patients treated with IR prazosin.

08.3 Prescription data

According to the IMS-EPPM [Permanent survey of medical prescription] data (moving annual total, autumn 2013), 3000 prescriptions were written for the proprietary medicinal product MINIPRESS. The small number of prescriptions for this proprietary medicinal product is insufficient to enable qualitative analysis of these data.

08.4 Summary and discussion

Primary efficacy data

The clinical data enabling the efficacy of immediate-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.

In the only available comparative study, ALPRESS (PR prazosin) versus MINIPRESS (IR prazosin), after 2 weeks of treatment, no difference was observed in terms of BP reduction or response rate between the two studied groups (statistical test not available).

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

Primary safety data

In the Materson study, 1995, which compared the efficacy and safety of six antihypertensive medicines used as monotherapy (hydrochlorothiazide 12.5 to 50 mg, atenolol 25 to 100 mg,

captopril 25 to 100 mg, clonidine 0.2 to 0.6 mg, PR diltiazem 120 to 360 mg and IR prazosin 20 mg) with a placebo in 1292 adults¹⁰ with mild to moderate hypertension (95<diastolic BP<109 mmHg), the adverse effects were most commonly encountered in the groups treated with clonidine (14%) and IR prazosin – MINIPRESS (12%).

Hypotension was observed in 12% of the patients treated with IR prazosin⁹ versus 8% in patients treated with clonidine and 5% in patients on the placebo. Even though hypotension was also observed with the PR release form (ALPRESS) like with the other antihypertensives, it was rare.

Discussion

The efficacy of immediate-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 immediate-release prazosin in terms of morbidity-mortality is currently available.

Even though the pharmacokinetic profiles of ALPRESS and MINIPRESS 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.

09 THERAPEUTIC USE

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 MINIPRESS:

Since alpha-blockers have not demonstrated their efficacy in terms of morbidity-mortality, they are only recommended as a last-resort treatment for rare patients with 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 objective.

Given the frequency of cases of hypotension observed with IR prazosin (MINIPRESS), only the PR forms are recommended for the long-term treatment of patients with arterial hypertension.

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

► 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 efficacy of prazosin demonstrated only in terms of blood pressure reduction and the unfavourable safety profile of the immediate-release form (MINIPRESS) in terms of the frequency of cases of orthostatic hypotension which are sometimes severe, especially at the start of treatment, its efficacy/adverse effects ratio is poorly established.

► Given the frequency of cases of hypotension observed with IR prazosin (MINIPRESS), only the PR forms of prazosin are recommended for the long-term treatment of patients with arterial hypertension, as a last-resort treatment for patients not controlled with any of the five classes of antihypertensives (alone or in combination) having demonstrated their efficacy in terms of morbidity-mortality.

Consequently, the Committee considers that the actual benefit of MINIPRESS remains insufficient in the "hypertension" indication.

The Committee does not recommend 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.

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Appendix
Summary of clinical studies: MINIPRESS (immediate-release prazosin)

Study	Method	Study population	Results
Torvik 19964	Controlled, randomised double-blind clinical study of prazosin 0.5 to 10 mg/day versus doxazosin 1 to 16 mg/day versus placebo. Follow-up: 12 weeks <u>Endpoints:</u> change in BP and HR	N=172 Patients with mild to moderate hypertension (96<diastolic BP<114 mmHg)	Change of the systolic BP/Diastolic BP: Prazosin: reduction of $-12 \pm 1.3/-10.4 \pm 1$ mmHg Doxazosin: reduction of $-14.2 \pm 1.7/-10 \pm 1$ mmHg Placebo: reduction of $-5.2 \pm 1.8/-4 \pm 1$ mmHg Significant difference versus placebo (NS between treatments)
Vanderburg 19835	Randomised clinical study prazosin then hydralazine Hydralazine then prazosin Prazosin + hydralazine Diuretic and beta-blocker add-on Follow-up: 8 weeks <u>Endpoint:</u> Multiple non-ranked endpoints (BP, HR, weight and symptoms)	N=36 Patients with mild to moderate essential hypertension (diastolic BP>90 mmHg).	Change of the BP Prazosin then hydralazine: reduction -13/-19 mmHg Hydralazine then prazosin: reduction -14/-17 mmHg Difference: NS Number of patients controlled (systolic BP<90 mmHg) Prazosin: 5 Hydralazine: 6 Prazosin + hydralazine 11 Descriptive analysis
Materson, 19956	Randomised, double-blind comparative clinical study HCTZ 12.56 à 50 mg/j Atenolol 25 to 100 mg/day Captopril 25 to 100 mg/day Clonidine 0.2 to 0.6 mg/day PR diltiazem 120 to 360 mg/day Prazosin 4 to 20 mg/day Placebo Follow-up: 8 weeks <u>Endpoint:</u> responder rate defined by diastolic BP<90 mmHg)	N=1292 Patients with mild to moderate arterial hypertension (95<diastolic BP<109 mmHg)	Responder rate (diastolic BP<90 mmHg) HCTZ: 55% Atenolol: 60% Captopril: 50% Clonidine: 62% Diltiazem: 72% Prazosin: 54% Placebo: 31% Descriptive analysis

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