

## Preterax®

### - Media Backgrounder -

#### About Preterax®

Preterax® is a first-line combination of perindopril and indapamide (2.0 mg perindopril / 0.625 mg indapamide).

Perindopril is an angiotensin-converting enzyme (ACE) inhibitor. Indapamide is a thiazide-related diuretic. The combination of an ACE inhibitor and a diuretic is amongst the most effective and rational combinations available for lowering blood pressure. The combination brings together the vasodilator and microcirculatory actions of an ACE inhibitor and the volume depletion of a diuretic, with each drug limiting the side effects of the other.<sup>1</sup>

#### Preterax in ADVANCE<sup>2</sup>

The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) study is the world's largest prospective mortality / morbidity trial in type 2 diabetic patients. The study aims to determine the effects of Preterax and an intensive glucose lowering Diamicon MR based therapy on the risk of complications in patients with type 2 diabetes mellitus.

Preterax was chosen as the blood pressure (BP) lowering reference drug for this study because of its safety and efficacy, as well as the recognised BP lowering and cardiovascular disease benefits demonstrated – particularly in diabetic patients.<sup>1</sup>

#### Efficacy

The efficacy of Preterax has been demonstrated in several key studies:

- Preterax the first-line combination containing perindopril and indapamide (2.0 mg perindopril / 0.625 mg indapamide) was shown to normalize significantly more patients than conventional

strategies recommended by the Guidelines<sup>3,4</sup> using the strictest BP criteria (SBP<140 and DBP<90 mmHg).

- In addition to this superior blood pressure control, Preterax has specific benefits, explained in part by its action on large arteries, and in part by its effects on the microcirculation.
  - The progressive stiffening of large arteries with age contributes to the dominant importance of systolic blood pressure as a predictor of cardiovascular risk, and to the difficulty of lowering systolic BP.<sup>5</sup>
  - The specific effects on the microcirculation were also demonstrated in particular in the Zucker rat, in which Preterax significantly improved renal perfusion. Those results were confirmed in hypertensive patients using PET Scan.<sup>6</sup>

The effects of Preterax on large vessels and on the microcirculation thus constituted further evidence of Preterax's efficient blood pressure reduction and target organ protection.

- Moreover, in a population of subjects with type 2 diabetes, Preterax was more effective in reducing blood pressure and albumin excretion than the reference drug and retarding the progression of cardiovascular diseases (*figure 2*).<sup>7</sup>

#### **Efficacy of perindopril alone and in combination**

- The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) showed that perindopril 4 mg and indapamide 2.5 mg (in free combination) reduced the risk of major vascular events (such as stroke and heart attack) by 40% in patients with a history of cerebrovascular disease.<sup>8</sup> In this study, both drugs showed excellent safety and tolerability profiles.<sup>8</sup>
- The EUROPA study (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) showed that perindopril (8 mg) is associated with a 20% reduction in the increase of the primary endpoint (heart attack, CV death or cardiac arrest) compared to placebo in high-risk patients with prior coronary heart disease (CHD).<sup>9</sup>
- The ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm) study reported that a regimen based on amlodipine and perindopril has been shown to be markedly superior to treatment with atenolol and bendroflumethazide at reducing all-cause

mortality and the incidence of major macrovascular events of renal failure and of new-onset diabetes.<sup>10</sup>

This is consistent with recent evidence from the Blood Pressure Trialists Collaboration that suggests that the reduction in major coronary events produced by ACE inhibitors such as perindopril is mediated in part through effects that are independent of blood pressure lowering.<sup>11</sup>

### Safety

A systematic review and meta-analysis of 11 trials (5936 individuals) found evidence that Preterax has a consistently favorable safety profile.<sup>12</sup>

- Ends -

### References

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<sup>2</sup>ADVANCE Collaborative Group. Study rationale and design of ADVANCE: action in diabetes and vascular disease-preterax and diamicron MR controlled evaluation. *Diabetologia*. 2001 Sep;44(9):1118-20.

<sup>3</sup>2003 European Society of Hypertension — European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens*. 2003;21:1011-1053.

<sup>4</sup>Mourad JJ, Waeber B, Zannad F, et al. Comparison of different strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. *J Hypertens*. 2004;22:2379-2386

<sup>5</sup>Mourad JJ, Hanon O, Deverre JR, Camici PG, Sellier P, Duboc D, Safar ME. Improvement of impaired coronary vasodilator reserve in hypertensive patients by low-dose ACE inhibitor/diuretic therapy: a pilot PET study. *JRAAS* 2003;4:94-95.

<sup>6</sup>Renaud I, Chainey A, Plante G, Chevalier J. Protection des structures et fonctions rénales chez le rat Zucker obese par l'association faiblement dosée perindopril/indapamide. *Arch Mal Cœur Vaiss*. 2002; 95

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<sup>8</sup>PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001 Sep 29;358(9287):1033-41.

<sup>9</sup>Fox KM, Henderson JR, Bertrand ME, *et al.* The European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA). *Eur Heart J.* 1998 Sep;19 Suppl J:J52-5.

<sup>10</sup>Dahlof B, Sever PS, Poulter NR, *et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet.* 2005 Sep 10-16;366(9489):895-906.

<sup>11</sup>Turnbull F, Neal B, Pfeffer M, Kostis J, Algert C, Woodward M, Chalmers J, Zanchetti A, MacMahon S. Blood Pressure Lowering Treatment Trialists' Collaboration. *J Hypertens.* 2007 May;25(5):951-8.

<sup>12</sup>Kang S, Wu YF, An N, Ren M. A systematic review and meta-analysis of the efficacy and safety of a fixed, low-dose perindopril-indapamide combination as first-line treatment of hypertension. *Clin Ther.* 2004 Feb;26(2):257-70.