Aggressive Goals Are Within Reach

Benicar® TABLETS (olmesartan medoxomil)

Benicar® HCT™ TABLETS (olmesartan medoxomil • hydrochlorothiazide)

GREAT BP REDUCTIONS FOR MORE AGGRESSIVE GOALS

In a clinical trial

BENICAR and BENICAR HCT helped a majorit

- According to NHANES, only 31% of patients with hypertension are controlled[1]

Nearly 7 out of 10 patients on BENICAR or BENICAR HCT reached the aggressive goal of ≤130/85 mm Hg and more than half of these patients did so on BENICAR monotherapy[2,3]

73% reached the aggressive SBP goal of ≤130 mm Hg[3]

87% reached the aggressive DBP goal of ≤85 mm Hg[3]

Overall mean baseline: 161/97 mm Hg

Adapted from Neutel et al. *Journal of Clinical Hypertension*. 2004.[3]

- Patients were titrated at 4-week intervals until they reached the goal of ≤130/85 mm Hg: BENICAR 20 mg, BENICAR 40 mg, BENICAR 40 mg + HCTZ 12.5 mg, BENICAR 40 mg + HCTZ 25 mg[2]

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, BENICAR or BENICAR HCT should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality** in the prescribing information.

f patients reach aggressive goals

- *JNC 7* guidelines establish more aggressive goals: treat most patients to BP <140/90 mm Hg; treat patients with comorbidities to BP <130/80 mm Hg[1]
- Landmark studies show patients require 2 to nearly 4 different agents to reach BP goal[2,3]

Majority of patients reached goal of ≤130/85 mm Hg on BENICAR or BENICAR HCT[2,3]

Stage 1 patients reached goal **89%**

***JNC 7* defines Stage 1 as SBP 140-159 mm Hg or DPB 90-99 mm Hg**

Stage 2 patients reached goal **54%**

***JNC 7* defines Stage 2 as SBP ≥160 mm Hg or DPB ≥100 mm Hg**

Mean baseline Stage 1: 150/95 mm Hg; Mean baseline Stage 2: 170/98 mm Hg

Adapted from Neutel et al. Journal of Clinical Hypertension 2004.

Open-label, multicenter 24 week titration trial (evaluable cohort, n=179). Patients who met entry criteria were initiated on BENICAR 20 mg QD. The end of study BP goal for all patients was ≤130/85 mm Hg. If the goal BP was not achieved, antihypertensive therapy was titrated at 4 week intervals according to the following step-wise algorithm until the goal BP was attained: up-titration of BENICAR to 40 mg QD, addition of HCTZ 12.5 mg QD, then up-titration of HCTZ to 25 mg QD, addition of amlodipine besylate 5 mg/d, and up-titration of amlodipine besylate to 10 mg/d. Percent of patients achieving goal based on 179 evaluable patients. Results presented are at Week 16, prior to the addition of amlodipine besylate.

BENICAR and BENICAR HCT are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents. BENICAR HCT is not indicated for initial therapy.

Please see full prescribing information for BENICAR and BENICAR HCT.

Benicar® TABLETS (olmesartan medoxomil)

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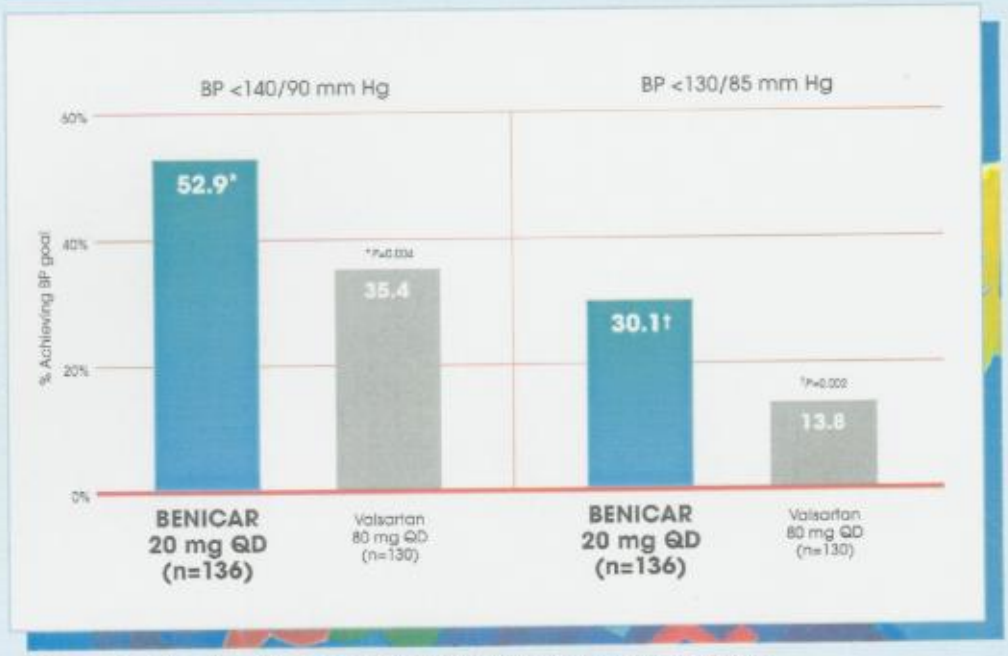
GREAT BP REDUCTIONS FOR MORE AGGRESSIVE GOALS

vs other ARBs

BENICAR monotherapy help

BENICAR starting doses: aggressive goal attainment vs valsartan[3,7]



Mean ambulatory baselines (mm Hg): BENICAR 152/94; valsartan 152/95

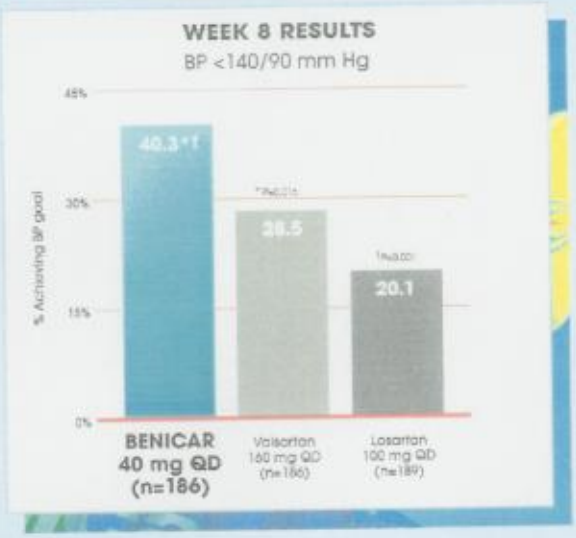
Ambulatory BP monitoring (ABPM) results based on secondary analysis at Week 8 from valsartan component. Part of multicenter, randomized, double-blind, parallel-group study. Overall control-rate comparison of BENICAR 20 mg QD (n=136) with losartan potassium 50 mg QD (n=134), valsartan 80 mg QD (n=130), and irbesartan 150 mg QD (n=134).

- In the same study, BENICAR 20 mg QD vs valsartan 80 mg QD achieved the following DBP cuff reductions: –11.5 mm Hg for BENICAR vs –7.9 mm Hg for valsartan ($P<0.0001$)[7]
  - — Mean cuff baselines (mm Hg): BENICAR 157/104; valsartan 155/104

Please see boxed **WARNING regarding use in Pregnancy** in the prescribing information for BENICAR and BENICAR HCT.

patients reach aggressive goals

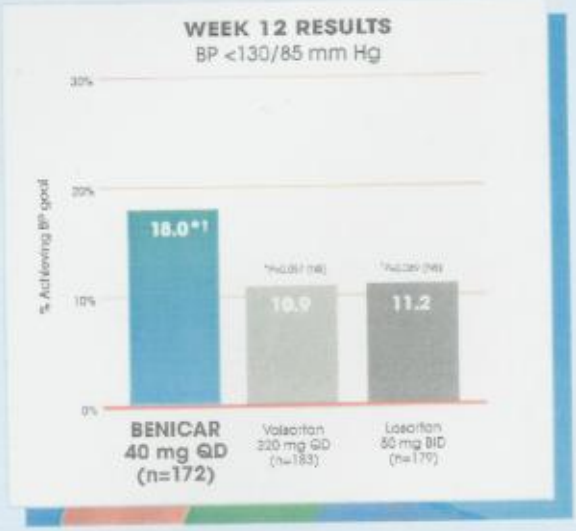
BENICAR titrated doses: aggressive goal attainment vs valsartan and losartan in patients with *Stage 2 Hypertension*[3]



Cuff BP control results (secondary analysis) of a 12-week, randomized, double-blind, forced-titration study (N=723) comparing the efficacy and safety of BENICAR versus valsartan, losartan potassium, and placebo in patients with Stage 2 hypertension. The primary endpoint was 8-week mean cuff DBP reductions. In this study, 22% of BENICAR patients, 19% of valsartan patients, 23% of losartan patients, and 22% of placebo patients were African American.

Results for placebo (n=90): 12.2%, P<0.001

At Week 8, mean BP reductions were superior to losartan ($P<0.001$) and similar to valsartan ($P=0.076$, NS).[3]



Week 12 data from second phase of study designed to show equivalence. See study description above.

Results for placebo (n=87): 2.3%, P<0.001

In the second phase of the study, designed to show equivalence, BENICAR dosing was maintained at 40 mg, valsartan dose was doubled to 320 mg and losartan dose was changed to 50 mg BID.[3] At Week 12, mean BP reductions were similar among the treatment groups.

Mean cuff baselines (mm Hg): BENICAR 156/104; valsartan 154/103; losartan 155/104; placebo 154/103

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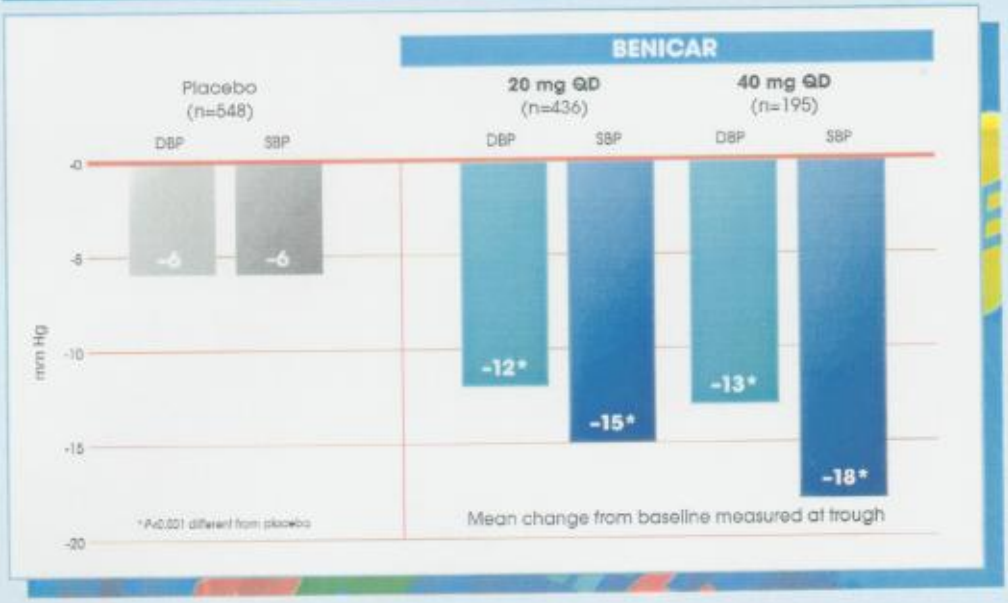
BenicarHCT™ TABLETS (olmesartan medoxomil • hydrochlorothiazide)

GREAT BP REDUCTIONS FOR MORE AGGRESSIVE GOALS

BENICAR monotherapy help

BENICAR provides mean double-digit BP reductions[3]

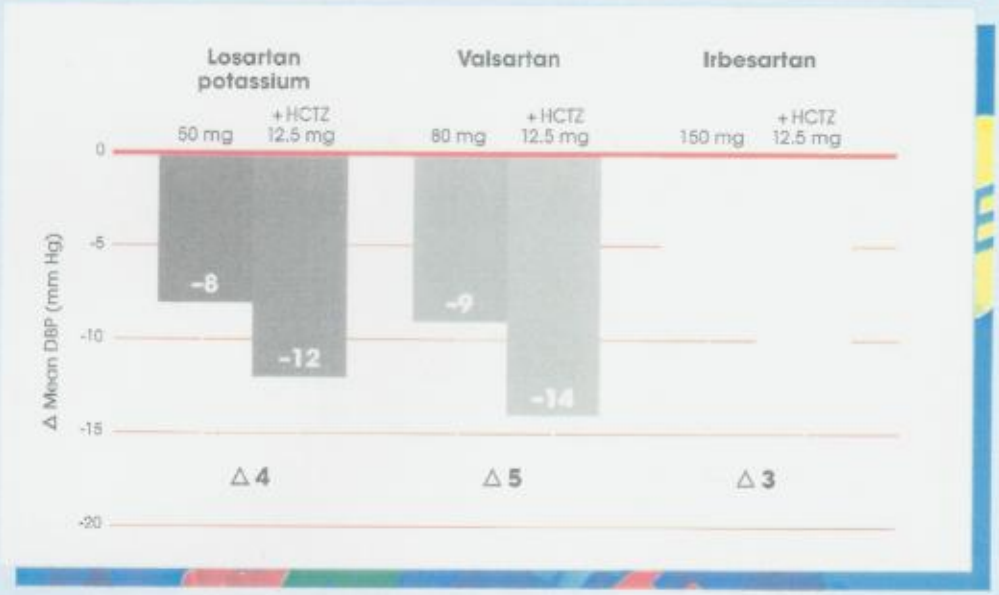


Study design Placebo and BENICAR sitting data. Derived from 7 dose-ranging studies. Duration=6 to 12 weeks. Patients taking BENICAR 2.5 to 80 mg, n=2145. Patients taking placebo, n=548.

Please see boxed **WARNING regarding use in Pregnancy** in the prescribing information for BENICAR and BENICAR HCT.

patients reach aggressive goals

DBP reductions when low-dose HCTZ added to 3 other ARBs[10]



Adapted from Conlin et al. *Am J Hypertens.* 2000.[10]

Pooled meta-analysis representing weighted average antihypertensive efficacy from 43 double-blind, randomized, controlled trials. Results compare DBP reductions using ARBs as starting-dose monotherapy, as monotherapy titration, and as ARB/HCTZ (12.5 mg) combination therapy. These results may vary from those reported in approved labeling.

ARB doses approximate most frequently prescribed.

66% to DBP goal

- Nearly 2 out of 3 patients on BENICAR monotherapy achieved the aggressive DBP goal of ≤85 mm Hg within 8 weeks in one titration or less in a clinical trial[2]
  —Mean baseline: 161/97 mm Hg

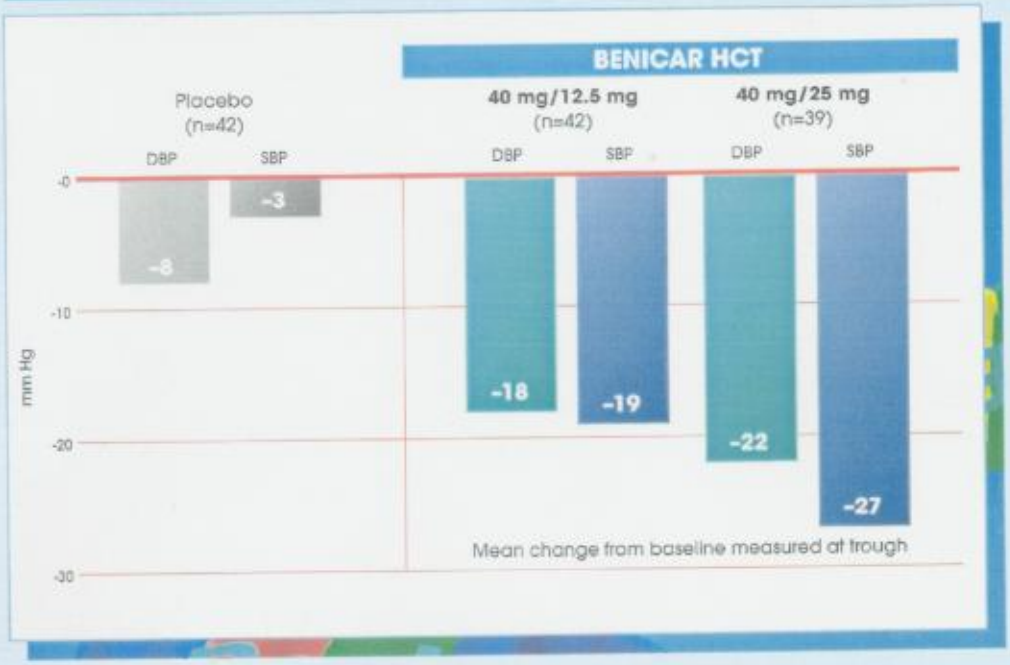
Benicar® TABLETS (olmesartan medoxomil)

Benicar HCT™ TABLETS (olmesartan medoxomil • hydrochlorothiazide)

GREAT BP REDUCTIONS FOR MORE AGGRESSIVE GOALS

Even more patients reach aggressive goc

BENICAR HCT provides significant mean double-digit reductions of up to 27 mm Hg SBP[12]



Mean baselines (mm Hg): Placebo 152/103; BENICAR + HCTZ 152-154/103-104

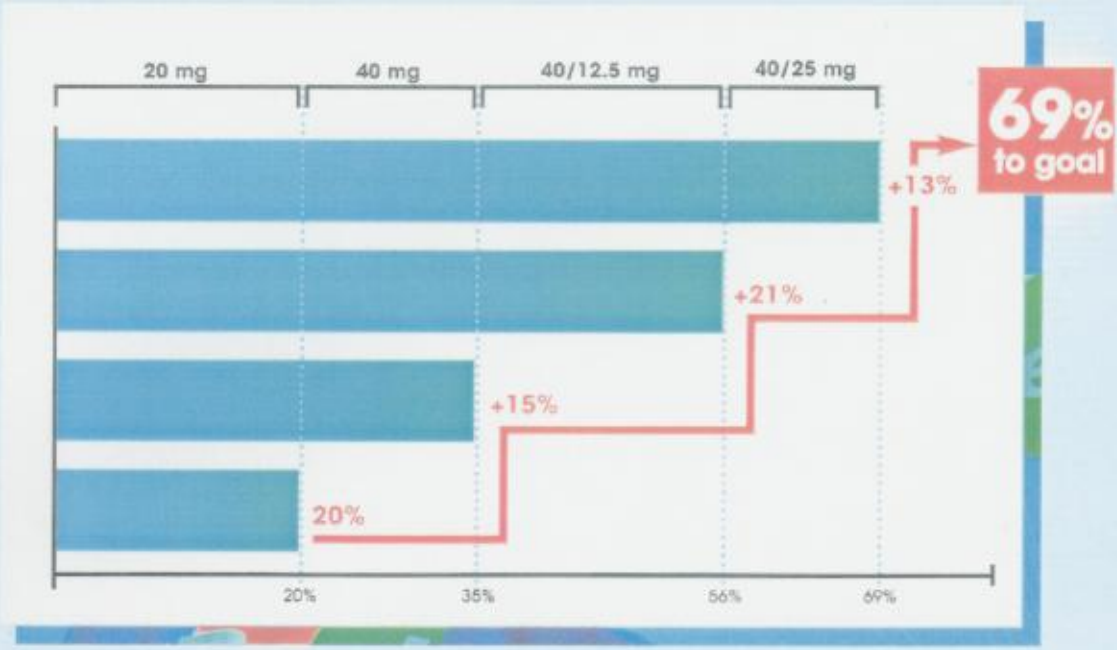
Adapted from Chrysant et al. *American Journal of Hypertension*. 2004.[12]

Placebo and BENICAR + HCTZ sitting data. A pivotal, randomized, double-blind, parallel-group, factorial study (N=502). Duration=8 weeks following a 4-week placebo run-in period.

Please see boxed **WARNING regarding use in Pregnancy** in the prescribing information for BENICAR and BENICAR HCT.

when HCTZ is added to BENICAR monotherapy

Titrating with BENICAR and BENICAR HCT got more patients to the aggressive BP goal of *≤130/85 mm Hg*[2,3]



Overall mean baseline: 161/97 mm Hg (n=179, nearly 70% were Stage 2 patients)

Adapted from Neutel et al. Journal of Clinical Hypertension. 2004.

Open-label, multicenter, 24-week titration trial (evaluable cohort, n=179). Patients who met entry criteria were initiated on BENICAR 20 mg QD. The end of study BP goal for all patients was ≤130/85 mm Hg. If the goal BP was not achieved, antihypertensive therapy was titrated at 4-week intervals according to the following step-wise algorithm until the goal BP was attained: up-titration of BENICAR to 40 mg QD; addition of HCTZ 12.5 mg QD; then up-titration of HCTZ to 25 mg QD; addition of amlodipine besylate 2.5 mg/d; and up-titration of amlodipine besylate to 10 mg/d. Percent of patients achieving goal based on 179 evaluable patients. Results presented are at Week 16 prior to the addition of amlodipine besylate.

More than half of the patients who reached goal of ≤130/85 mm Hg on BENICAR or BENICAR HCT were controlled on BENICAR monotherapy[2,3]

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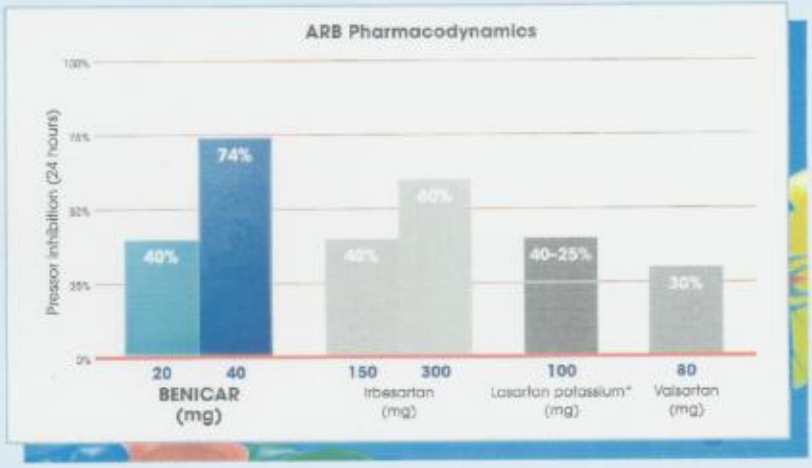
GREAT BP REDUCTIONS FOR MORE AGGRESSIVE GOALS

BENICAR HCT/TG Titration

PK Profile/Safety/HOT Trial

Reaching aggressive BP goal

BENICAR blockade of BP-raising effect of angiotensin II at 24 hours vs other ARBs[3]



Percentage inhibition based on current package inserts; all agents administered as a single dose.

No information on effect of larger doses of valsartan was available.

Losartan inhibition ranged between 25% and 40%.

Pressor inhibition refers to the blockade or interruption of any BP-raising mechanism in the body, including blockade of angiotensin I. Angiotensin II is a major contributor to vasoconstriction, which is a principal component of hypertension.

*Titrated dose.

- BENICAR 40 mg inhibited 74% of the BP-raising effect of angiotensin II at 24 hours[3]

ARB pharmacokinetic parameters[1]

ARB	Half-life (Hours)	Time to Maximum BP Effect[2] (Weeks)	P450 Metabolism	Elimination (Approximations)
BENICAR	**13**	**2**	**NO**	**35%-50% renal 50%-65% hepatobiliary**
Irbesartan	11-15	2	Yes (CYP 2C9)	20% renal 80% hepatobiliary
Losartan potassium	6-9	6	Yes (CYP 2C9 and 3A4)	35% renal 60% hepatobiliary
Valsartan	6	4	Unknown	13% renal 83% hepatobiliary

[1]Based on current package inserts. [2]From clinical trials.

Clinical significance of pharmacodynamic and pharmacokinetic data is unknown.

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Benicar® TABLETS (olmesartan medoxomil)

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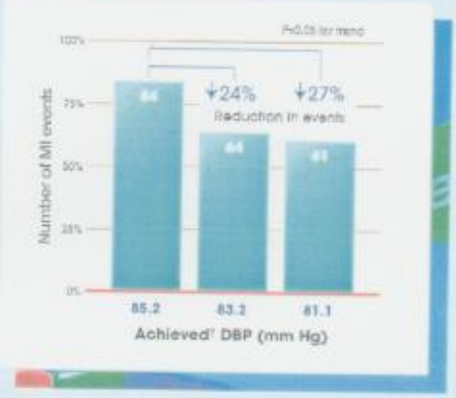
GREAT BP REDUCTIONS FOR MORE AGGRESSIVE GOALS

with BENICAR

The Hypertension Optimal Treatment (HOT) trial confirms: reaching BP goals is essential[13]

Lower diastolic blood pressure associated with fewer MIs*



Randomized, multinational study
N = 18,790 hypertensive patients. Baseline DBP = 105-115 mm Hg. Study delineates the association between major CV events and a treatment goal: 1) ≤90 mm Hg, 2) ≤85 mm Hg, 3) ≤80 mm Hg. Classes of studied drugs included: calcium channel blockers, ACE inhibitors, beta blockers, and diuretics.

Adapted from Hansson et al.[13]

*MI = myocardial infarction.
†Achieved spread of all BPs from 6 months' follow-up to end of study.

The great efficacy of BENICAR and BENICAR HCT—combined with favorable safety and tolerability

In clinical trials:

- The withdrawal rates due to adverse events (AEs) were similar with BENICAR and BENICAR HCT to placebo: BENICAR (2.4% vs 2.7%); BENICAR HCT (2.0% vs 2.0%)
- The incidence of AEs with BENICAR and BENICAR HCT was similar to placebo
  - The only AE that occurred in >1% of patients treated with BENICAR and more frequently than placebo was dizziness (3% vs 1%)
  - AEs reported in >2% of patients taking BENICAR HCT and more frequently than placebo included nausea (3%), hyperuricemia (4%), dizziness (9%), and upper respiratory tract infection (7%)
- No initial dosage adjustments necessary with BENICAR in elderly or in moderate to marked renal impairment†/hepatic dysfunction
  - In patients with possible depletion of intravascular volume (eg, patients on diuretics, particularly with impaired renal function), BENICAR should be initiated under close medical supervision and consideration given to use of a lower starting dose

†Creatinine clearance <40 mL/min.

- BENICAR HCT is not recommended in patients with severe renal impairment and is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs

Prescribe the Fastest-Growing ARB[1,4]

Aggressive Goals Are Within Reach

In a clinical trial

More patients on BENICAR and BENICAR HCT reached aggressive goals

69% of patients on BENICAR or titrated up to the maximum dose of BENICAR HCT reached the aggressive goal of ≤130/85 mm Hg[2]

- **—89% of Stage 1** patients reached goal
- **—54% of Stage 2** patients reached goal

More than half the patients who reached the aggressive goal of ≤130/85 mm Hg on BENICAR or BENICAR HCT were controlled on BENICAR monotherapy[3]

Other trials demonstrate excellent monotherapy goal attainment vs other antihypertensives[3,7,8]

Even more patients reached aggressive goals when HCTZ was added to BENICAR monotherapy

BENICAR—available to more than 93% of HMO/PBM lives[3]

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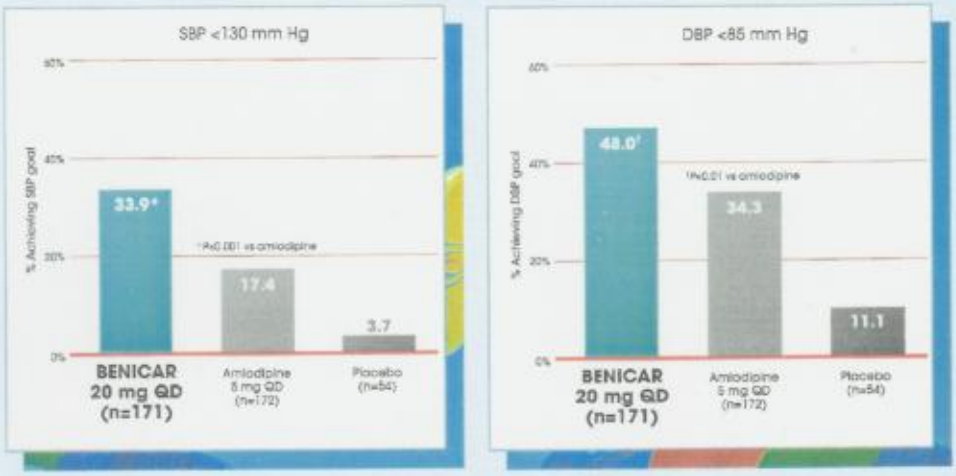
More BENICAR patients achieved aggressive BP goals than patients on amlodipine[6]

Chrysant Study[6]



Adapted from Chrysant et al. *Journal of Human Hypertension*, 2003.[6]

Ambulatory BP control results (a secondary endpoint) from 8-week, randomized, double-blind, placebo-controlled study (N=440) of patients with mild-to-moderate hypertension. Study drugs given at recommended starting doses.

Mean ambulatory baselines (mm Hg): BENICAR 154/96; amlodipine besylate 154/95; placebo 154/96

- BENICAR, at the starting dose of 20 mg QD, provides mean double-digit BP reductions vs baseline similar to amlodipine at the starting dose[6]
  - — 10.3/10.8 mm Hg reductions with BENICAR
  - — 10.3/10.1 mm Hg reductions with amlodipine
  - — Mean cuff baselines (mm Hg): BENICAR 155/104, amlodipine 155/104, placebo 154/103

A second study vs the CCB felodipine yielded similar results in mean BP reductions.[9]

References:

1. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. *JAMA*. 2003;290:(No.2):199-206. **2.** Neutel JM, Smith DHG, Weber MA, Wang AC, Masonson HN. Use of an olmesartan medoxomil-based treatment algorithm for hypertension control. *J Clin Hypertens*. 2004;6:168-174. **3.** Data on file, Sankyo Pharma Inc., Parsippany, NJ. **4.** *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. Bethesda, Md: National Institutes of Health: National Heart, Lung, and Blood Institute: National High Blood Pressure Education Program: May 2003. NIH publication 03-5233. **5.** Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens*. 2002;4(6):393-404. **6.** Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis*. 2000;36(3):646-661. **7.** Oparil S, Williams D, Chrysant SG, Marbury TC, Neutel J. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. *J Clin Hypertens*. 2001;3:283-291. **8.** Chrysant SG, Marbury TC, Robinson TD. Antihypertensive efficacy and safety of olmesartan medoxomil compared with amlodipine for mild-to-moderate hypertension. *J Hum Hypertens*. 2003;17:425-432. **9.** Stumpe KO, Ludwig M. Antihypertensive efficacy of olmesartan compared with other antihypertensive drugs. *J Hum Hypertens*. 2002;16(suppl 12):S24-S28. **10.** Conlin PR, Spence JD, Williams B, et al. Angiotensin II antagonists for hypertension: are there differences in efficacy? *Am J Hypertens*. 2000;13:418-426. **11.** IMS Health, National Prescription Audit, January-December 2003. **12.** Chrysant SG, Weber MA, Wang AC, Hinman DJ. Evaluation of antihypertensive therapy with the combination of olmesartan medoxomil and hydrochlorothiazide. *Am J Hypertens*. 2004;17:252-259. **13.** Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998;351:1755-1762. **14.** IMS Health, National Prescription Audit, March 2004 vs December 2003.