Hypertension management evolving through the ages

“...If too much salt is used in food, the pulse hardens.” — Huang Ti Nei Ching Su Wen, 2674 BCE

Following a welcome address from ASH President Henry R. Black, MD, Eugene Braunwald, MD began Sunday’s keynote address, “Hypertension: The Past — The Present — The Future.” With this quote from an ancient Chinese treatise on internal medicine, Dr. Braunwald, a renowned Harvard cardiologist, also noted that Su Wen said that “the heart rules over the kidneys,” but was also quick to point out that cardiologists are first cousins with hypertension specialists.

Now let’s leap forward several thousand years to the first half of the nineteenth century, eight thousand miles east in London. Richard Bright was a senior physician at Guy’s Hospital, when he made some classical pathological and clinical correlations, Dr. Braunwald said. “He demonstrated the association between albuminuria, dilution of the specific gravity of the urine, and shrinking and hardening of the kidneys.”

Thus began a line of research that has led not only to the understanding of hypertension but also to effective clinical means in its management.

The first crude objective measurements of blood pressure were made by Frederick A. Mahomed using a research tool, which measured the external pressure required to obliterate the pulse.

“This paper by Mahomed is one of the most important, yet most neglected papers in the history of medicine,” said Dr. Braunwald. “It describes what he called the pre-albuminuric phase of Bright’s disease, a condition we now call essential hypertension.”

Subsequent discoveries lead to an understanding of the renin-angiotensin system, the accurate measurement of systolic and diastolic pressures, and effective pharmacological approaches in treatment.

“I cannot even attempt to cover the development of all the antihypertensive products, which I consider to be one of the major success stories of twentieth century medicine. I will show you just two,” he said.

In 1962, James Black, a scientist at Imperial Chemical Industries synthesized and studied nethalide, the first adrenergic beta-receptor blocking compound. “I nominated Black, first for an honorary degree at Harvard and then for the Nobel prize. He was one of the few industry scientists to receive this award. Black died just two months ago,” said Dr. Braunwald.

In addition, in 1977 David Cushman and Miguel Ondetti described the first orally active angiotensin-converting enzyme inhibitor.

Currently, combination therapies are showing improved efficacy over monotherapy, and epidemiological studies are illuminating the global burden of blood pressure-related disease as well as the importance of identifying and treating hypertension.

Novel approaches now being explored include electric field stimulation of carotid sinus baroreflex afferents that has shown acutely decreased arterial blood pressure in hypertensive patients.

Experts to discuss use of pulse wave velocity, central aortic pressure in reducing CV risk stratification

Four years ago, the Association for Research into Arterial Structure and Physiology (ARTERY) was founded in the United Kingdom. Since then, the organization has generated interest and developed relationships with many U.S. physicians — ASH members, in particular.

Given the collegial nature of the relationship between ASH and ARTERY, it was only natural for the two groups to collaborate on a joint session for the ASH 25th Annual Scientific Meeting.

The session, “Assessing Arterial Stiffness to Improve the Management of Cardiovascular Disease in the 21st Century,” will take place from 10:00 to 11:30 a.m., today, Monday, May 3, in Sutton North.

ARTERY President John R. Cockcroft, MD, of Cardiff, United Kingdom, said the overall goal of the session is to present the evidence for measuring such parameters as pulse wave velocity and central aortic pressure to improve cardiovascular risk stratification.

Epidemiological data will be presented to show that measuring pulse wave velocity improves risk stratification beyond the Framingham risk score. Furthermore, a number of trials have also shown that central aortic blood pressure is a better predictor of outcome than brachial pressure.

What remains unclear, Dr. Cockcroft said, is whether targeting aortic pulse wave velocity and central blood pressure will improve cardiovascular outcomes beyond that achieved by reduction of brachial pressure.

“In order to best achieve this, it is essential to understand the pathophysiological mechanisms involved in increasing arterial stiffness and central blood pressure,” he said.

The session will include new data on meta analyses of both aortic pulse wave velocity and central blood pressure and outcome. In addition, the latest data on the effects of inflammation and genetics on
A Cross-Examination of Contemporary Issues
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Monday, May 3, 2010

Registration and Dinner: 7:00 PM - 7:30 PM
Symposium: 7:30 PM - 9:00 PM
Trianon Ballroom, Hilton New York

Today’s Controversy and Consensus

Program Overview
Take part in a “clinician’s courtroom” where 2 faculty “counselors” cross-examine opposing sides of contemporary issues in hypertension. The proceedings will be moderated by the “Judge” who will challenge the counselors to document their statements and consider objections from opposing “Counsel” as well as the audience. The audience plays the part of the jury and will be asked to render a verdict based on the data that are presented.

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University of Chicago Medical Center
Chicago, IL

Faculty
Domenic A. Sica, MD
Head, Section of Clinical Pharmacology and Hypertension
Virginia Commonwealth University
Richmond, VA

William B. White, MD
Professor, Department of Medicine
University of Connecticut Health Center
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Agenda:

Debate #1: Setting treatment goals in hypertension care
Case Study Discussion: Combining blood pressure-lowering agents and emerging treatment options
Debate #2: Using biomarkers to assess risk in hypertension patients

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Blood pressure (BP) readings may vary from clinical measurements when performed by patients at home. This can stem from white coat hypertension, or conversely, masked hypertension, both of which may have important ramifications.

Angela L. Brown, MD, began Sunday’s ‘Hypertension for the Primary Care Physician 2010’ by discussing these entities. “White coat hypertension is when the patient says, ‘Doc, my blood pressure at home is always OK, it’s only high when I come to your office’. You really need to sort that out,” said Dr. Brown.

More common in the elderly and accounting for about 20 percent of diagnosed hypertensive patients, white coat hypertension is defined as persistently elevated office BP and normal BP at other times. “Masked hypertension is a group that is a little more difficult to identify. These are the folks whose office blood pressures are normal but are actually elevated outside the office,” she said. “But unlike white coat hypertension, there actually may be some predictive significance for developing hypertension and having increased cardiovascular risk.”

These patients, whom represent about 10 percent of diagnosed hypertensive patients, tend to have a higher ambulatory pulse rate, be more obese and have a parental history of hypertension as compared to normotensive patients. “Masked hypertension seems to have a much different prognosis than what we’ve seen with white coat hypertension,” Dr. Brown said.

Twenty-four hour ambulatory monitoring was deemed prudent should either white coat or masked hypertension be suspected. “Without necessary treatment of white coat hypertension was of concern, there exist more consequences should masked hypertension be overlooked due to a similar risk profile as sustained hypertension,” William B. White, MD, then discussed the benefits of 24-hour ambulatory and home blood pressure monitoring. “I like the fact that self-monitoring makes the patients more involved in their care more than anything else. People who do home blood pressure measurements consistently have better hypertensive control than those who don’t do it,” said Dr. White.

A case was presented of a 78-year-old male on antihypertensive therapy with office BP of 154/74 mm/Hg at his afternoon checkup. Home monitoring then exposed morning BP of 180-190/110 mm/Hg and afternoon BP of 150/90-95. “He told his physician about it; his physician said don’t worry, your blood pressure was normal in my office. You have nothing to worry about,” Dr. White said. “He didn’t like that answer.”

Subsequent 24-hour ambulatory monitoring revealed moderate afternoon hypertension, but of more significance, masked hypertension in the last six hours of the dosing period. Alteration in dosing produced consistent normotensive values, thereby greatly reducing cardiovascular risks during the hypertensive spikes.

Other factors may come into play. “Why would somebody have such a great blood pressure in your environment, and he hypertensive elsewhere? Well, there are actually some people who love us — not many — but a few,” he said.

In addition, patients may be returning to stressful situations and work or home and find the office visit soothing.

Elderly patients often present with isolated systolic hypertension (ISH) caused by tissue changes related to the aging process.

“The database program will evaluate global risk scores for patients at baseline and on a regular basis for a total of five years, during which we’ll record prospectively the number of events of coronary heart disease, myocardial infarction, stroke, and heart failure,” Dr. Roccella said. “This data will be processed and correlated in order to determine the most efficacious ways to approach the issue of reducing morbidity and mortality in the United States and the southeastern States, in particular.”

However, the database information can do more than serve as a tool for tracking risk factors, treatments, and improvements. COSEHC Board Member Edward J. Roccella, PhD, MPH, of the National Institutes of Health’s National Heart, Lung, and Blood Institute, said the COSEHC database is an invaluable tool for personalized, targeted patient education, communication, and community outreach.

“I’ve been in this business for 32 years, and I can tell you that these guys are on to something big,” he said. “This is going to change blood pressure prevention and control.”

Steven A. Yarrows, MD, began ‘Hypertension in the Elderly’ by explaining how ISH is a different entity than mixed systolic/diastolic hypertension.

It’s easy to control diastolic hypertension in 99 percent of the patients. If you can’t control systolic hypertension, then join the crowd, because it is very hard to control,” said Dr. Yarrows.

After about the age of 50, systolic pressure tends to elevate as diastolic begins to decrease. During systole, normal physiology involves 40 to 50 percent of the stroke volume is forwarded directly to the peripheral tissues, with the remainder stored in the distended aortic and central arteries. This changes a pulsatile flow into a more continuous flow.

The large arteries become stiffer with age. “Isolated systolic hypertension is a conduit disease problem. Diastolic hypertension is a small arterial resistant disease. It is a different mechanism of disease,” he said.

Hypertension is a costly disease due to cardiovascular complications, thus controlling hypertension is one of the most cost effective forms of medical intervention.

Organizations demonstrates regional, targeted approach to BP control, improving CV outcomes

Communities nationwide struggle with the growing epidemics of obesity, diabetes, hypertension, and more, and these problems translate into poor cardiovascular outcomes for a large percentage of Americans.

According to the American Heart Association, more people are dying of heart disease and stroke than any other cause of death. “Unfortunately, these individuals do not contribute to something big,” he said. “This is going to change blood pressure prevention and control.”

For many physicians, it would be impossible to do all of these things for all patients. However, with the information in the COSEHC database and such communication tools as email, facebook, twitter, blogs, webinars, and so on, physicians can construct targeted messages aimed at unique patient populations in an efficient way.

Monday | Tuesday • 25th Anniversary • ASH Times
Session to include new recommendations for African American hypertensive patients

Several years ago, ASH began collaborating with the International Society on Hypertension in Blacks (ISHIB) to offer joint symposia during annual meetings. The trend continues this year when the ISHIB will present the “Consensus Update to ISHIB Management Guidelines,” which will take place from 8:00 to 9:30 a.m. on Tuesday, May 4, in Beekman Parlor.

Presenter John M. Flack, MD, MPH, of Detroit, Michigan, said it makes good sense for ASH and the ISHIB to cooperate and collaborate, and he hopes the relationship continues into the future.

Dr. Flack, who will present an “Overview of the Updated ISHIB Guidelines” during the symposia, said that writing guidelines for hypertension in African Americans is a bit difficult because of the lack of data in many areas.

“So the route we took was to write a consensus statement, which is as evidence-based as we can make it, but also borrows from expert opinion as well as extrapolates data from other racial and ethnic groups in important areas of decision-making that we need in order to make recommendations in the African American hypertension population,” he said. “We’ve looked at blood pressure goals or target levels, justification for target levels in lower-risk as well as higher-risk patients. We’ve looked at — and will make recommendations on — how you should use target levels.”

Dr. Flack said one thing the ISHIB has emphasized is using blood pressure goals as a ceiling — not a floor.

“I think a lot of people shoot to get someone barely under goal,” he said. “But if you’re going to set a goal — and it’s a goal you want to keep them under given the inherent variability of blood pressure — you need to get them below their goal by some principle amount to ensure that they stay there.”

Dr. Flack said he believes the ISHIB has devised a consensus statement that will provide maximum risk reduction without being overzealous or underzealous for low- and high-risk individuals.

Following Dr. Flack’s presentation, Richard H. Grimm Jr., MD, PhD, of Minneapolis, Minnesota, will review the clinical trial data that supports the updated recommendations. Then Brent M. Egan, MD, of Charleston, South Carolina, will discuss how these updates can and should be implemented in clinical practice.

The session will conclude with a panel discussion.

Experts will explore links between heart, kidney in blood pressure control

Today morning, Tuesday, May 4, three experts will examine “Cardiovascular and Kidney Outcomes in Heart Failure” as part of a joint session in partnership with the Inter-American Society of Hypertension (IASH).

The session will take place from 8:00 to 9:30 a.m. in Sutton South.

Session chair L. Gabriel Navar, PhD of New Orleans, Louisiana, said the IASH was formed in 1973 to stimulate and nurture hypertension and cardiovascular-related research in Latin America.

“It’s a col-legislation organization,” he said.

“The IASH has members from Canada all the way to Argentina and Chile. There’s a lot of active research happening in Brazil, Argentina, Mexico, Chile and other Latin American countries.”

The society’s primary mission is to improve and increase hypertension awareness and research throughout the Americas and to serve as a bridge or a conduit for the exchange of ideas among scientists from various countries across the Americas.

With that in mind, three experts will present lectures on cardiovascular and kidney outcomes in patients with heart failure during the joint session.

“There’s growing awareness that heart failure is associated with an increased incidence of kidney disease, just as kidney disease is associated with increased incidence of heart failure and other cardiovascular diseases,” Dr. Navar said. “We thought this was a good way to explore the interactions between these two organs because they are so tightly linked in the control of blood pressure.”

There’s growing awareness that heart failure is associated with an increased incidence of kidney disease, just as kidney disease is associated with increased incidence of heart failure and other cardiac diseases.

“We know that heart failure as the initiating cause of kidney disease will illicit a number of different responses and require adaptive changes in the kidney to cope with the heart failure,” Dr. Navar said. “So we first want to address the issue of what happens to kidney function with a failing heart.”

Then Scott D. Solomon, MD, of Boston, Massachusetts, will discuss diastolic versus systolic dysfunction. Domenic A. Sica, MD, will wrap up the session by addressing clinical concerns, including how to address blood pressure control in heart failure and kidney failure.

“Each of these three 30-minute sessions will focus on the interactions of these two organs and how a failing heart will affect kidney function and how kidney disease will affect heart function,” Dr. Navar said.

What the Hypertension Specialist Should Know

Back by popular demand, this series will feature presentations on topics important to the Hypertension Specialist. Following the presentations will be a “Meet the Expert” session on the same topic allowing participants to engage in further dialogue with the speakers.

MONDAY’S SCHEDULE

Renal Mechanisms of Hypertension∗

9:45 a.m. — What the Hypertension Specialist Should Know About Renal Sympathetic Nerves

Gerald F. Dilma, MD, Iowa City, IA

Cardiometabolic Syndrome ∗

East Ballroom

11:00 a.m. — What the Hypertension Specialist Should Know About Metabolic Syndrome and Polycystic Ovary Syndrome

David A. Ehrmann, MD, Chicago, IL

Complications of the Hypertensive Disease Process ∗

West Ballroom

11:00 a.m. — What the Hypertension Specialist Should Know About the Treatment of Atrial Fibrillation in the Hypertension Patient

Peter R. Kowey, MD, Wynnewood, PA

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Joint session brings Chinese experience to physicians in the United States

During the 2009 ASH Annual Scientific Meeting, the Society invited the China Social Worker’s Association Vascular Protection Committee to present a joint session. Session co-chair Hongyu Wang, MD, PhD, of the Cardiology Vascular Disease Early Detection Center in Beijing, said the success of that endeavor lead to further cooperation between the two organizations.

As part of this cooperation, a second joint session, “Early Vascular Disease Detection and Management: Experience from China,” will take place from 8:00 to 9:30 a.m., Tuesday, May 4, in Sutton North.

Dr. Wang will present the first of several lectures, “Vascular Disease Control and Early Prevention in China,” during which he will share strategies that have been used in China to study, detect, and prevent vascular disease.

“This collaborative strategy allows our organizations to exchange new knowledge about vascular health protection from each of our countries,” Dr. Wang said. “Vascular disease is the leading cause of the poor health worldwide. Only by early vascular disease detection and prevention can we effectively reduce morbidity and mortality of vascular events. A close relationship between our two groups will help experts from our two countries deeply understand the field of vascular medicine and promote it widely around the world.”

Dr. Wang said the ultimate goal of these joint sessions is to effectively reduce vascular events both in developed and developing countries.

“We hope to share our experiences about vascular health protection with each other and to promote communication among physicians in our countries in an effort to improve the health of Western and Eastern populations,” he said.®
Automating Healthcare — Can optimal blood pressure control be computerized?

Studies presented at ASH 2010 test the effectiveness of electronic health records and automated performance measures to control blood pressure and cut the risk of death.

NEW YORK, May 3, 2010 — Electronic health records (EHR) with controlled interventions can produce optimal blood pressure (BP) control and reduce mortality, according to data being presented Monday, May 3, during the ASH Annual Scientific Meeting and Exposition.

As one in three American adults now has high blood pressure, improving hypertension control rates has become a top priority for healthcare organizations in the United States and around the world. Numerous approaches have been employed to improve blood pressure control, including increasing patient involvement, improving patient compliance, reversing physician inertia, improving life style modifications, and optimizing pharmacologic therapy. The use of EHR has made it possible to follow large numbers of patients long-term and monitor the impact of these interventions.

“The proven benefits of blood pressure treatment and control, effective clinical models to control hypertension remain elusive,” said Henry R. Black, MD, President of the American Society of Hypertension. “This evidence-based research is crucial, but the challenge remains how to effectively incorporate these systems into the clinic.”

In the presented studies, researchers evaluated data collected by the Veterans Health Administration EHR system. The system has integrated performance measures and specific automated reminders that prompt caregivers to control BP until levels below 140/90 mm Hg are achieved. All vital signs recorded in each facility are available in a common database allowing analyses to be made using actual BP readings.

In a large, eight-year study of patients from 15 Department of Veterans Affairs Medical Centers, researchers assessed the effect of organized interventions to control BP. The study population included 476,191 hypertensive patients (BP above 140/90 mm Hg dysfunction, and reduces) and 173,946 patients with normal BP. Investigators found that overall yearly control of BP increased by 3.7 percent per year (p < .0001; 95% CI, 3.3-4.0). At the end of the follow-up period, more than 70 percent of hypertensive patients were controlled. At some centers, control was above 80 percent. The mean percent of controlled patients increased across all ethnic groups: from 52.9 to 64.2 percent in African Americans; 55.4 to 73.0 percent in Caucasians; and 49.3 to 74.6 percent in Hispanics.

Control rates also improved across all age groups: for patients <55 years of age control rates increased from 49.5 percent to 69.9 percent; for patients aged 55 to <70 from 49.6 percent to 70.9 percent; patients aged 70 to <80 increased from 43.5 percent to 72.3 percent; and patients older than 80 increased from 44.0 percent to 71.6 percent (p<.0001 for all groups).

When closely monitoring BP control over time, comparing winter and summer readings can show misleading improvement or worsening because of seasonal variations in BP, especially among hypertensive patients. Accordingly, investigators specifically analyzed seasonal variation in control rates and found that the percent controlled was six percent higher in summer than winter on average (p=.0001; 95% CI, 5.7-6.3). While seasonal variation produces a winter dip in control, the effect was blunted when elevations were rapidly brought under control using revisits to clinics every two weeks.

“With the use of a uniform system for controlling blood pressure aimed at the blood pressure level itself, organized intervention produced high rates of control in all ethnic and age groups in all cities,” said study author Ross D. Fletcher, MD, Chief of Staff, VA Medical Center, Washington, DC. “However, while a computerized system helped evaluate the rates of control, it remains the caregiver’s responsibility to determine the appropriate interventions for each individual patient.”

A sub-study conducted in the Washington, DC Veterans Affairs Medical center evaluated the impact of optimal BP control on mortality. Investigators found that a user-friendly, searchable, computerized patient record system (CPRS) could help achieve high rates of BP control and be maintained long-term to provide substantial improvement in mortality risk.

In the eight-year study, evaluating 62,346 patients with multiple readings, BP control (<140/90 mm Hg) increased from 44 percent to 76 percent. Investigators divided patients, based on the frequency and success of BP control, into six groups to assess mortality risk:

- G1: never hypertensive (n=4,459)
- G2: hypertensive always controlled (n=1,305)
- G3: BP elevated 1-25% of the time (n=8,160)
- G4: BP elevated 26-50% of the time (n=5,944)
- G5: BP elevated 51-75% of the time (n=8,045)
- G6: BP elevated 76-100% of the time (n=8,045)

At 90 months of follow-up, mortality rates were as follows: G1: 3 percent, G2: 9 percent, G3: 9.2 percent, G5: 10 percent, and G6: 11.2 percent (p<.0001 for the trend). Results were adjusted for age, sex, heart failure, diabetes mellitus, and body mass index (BMI). Comparing the optimal BP control group (G2) to poorly controlled BP control (G6), there was a 47 percent reduction in all cause mortality.

“We conclude that high rates of blood pressure control can be achieved in a usual clinical practice setting and can be maintained long term,” said lead researcher Vasilios Papademetriou, MD, Veterans Affairs Medical Center, Georgetown University. “Optimal blood pressure control provided substantial improvement in mortality risk and even partial blood pressure control provided significant mortality risk reduction.”

Increased cardiac mass called an ‘enemy of the kidneys’

New data suggest increased left ventricular mass has an independent impact on kidney dysfunction.

NEW YORK, May 3, 2010 — Data being presented Monday, May 3, at the ASH 25th Annual Scientific Meeting and Exposition indicate that in men with high cardiovascular risk, left ventricular mass may help better predict future cardiovascular and renal outcomes, including hemodialysis. Left ventricular hypertrophy (LVH) is becoming exceedingly common in patients with renal disease and reducing the incidence of end-stage renal disease is widely recognized as a major public health goal given the adverse social and economic costs of hemodialysis. Additionally, a substantial amount of evidence has documented a strong association between impaired kidney function and adverse cardiovascular events, including myocardial infarction and stroke.

In this retrospective study evaluating more than 6,000 men (mean age 68 years, the majority being hypertensive) for a period of 14 years, investigators assessed left ventricular mass index (LVMI) at baseline and kidney function and blood pressure levels at baseline and at the end of the follow-up period.

A strong association of LVMI for both body surface area and height on all of the examined renal outcomes (i.e. doubling of serum creatinine, retinopathy and estimated glomerular filtration rate below 60mL/min/1.73m2 and incident hemodialysis) was observed. For each 2 g/m2 increase in LVMI there was a rise in the risk of all renal outcomes by: 45.7 percent for doubling of serum creatinine; 51.9 percent for estimated glomerular filtration rate < 30 mL/min/1.73m2; and 58.5 percent for hemodialysis. Moreover, patients with at least moderate grade LVH (left ventricular mass index more than 125g/m2) showed a marked decline of kidney function when compared with those without (left ventricular mass index below 110g/m2).

In men with high cardiovascular risk, the severity of LVH could be a useful clinical tool in determining the decline of kidney function, including the increased probability for hemodialysis,” said study author, Costas Tsipoudis, MD, Professor of Medicine in the Cardiology Department at the Veterans Affairs Medical Center in Washington, DC. “These results underline that at least moderate cardiac hypertrophy substantially accelerates the development of adverse renal outcomes, further suggesting that minor degrees of hypertrophy could constitute the appropriate time period to act for protecting kidneys from progressive impairment.”
Monday at the ASH Hypertension Resource Pavilion

The ASH Hypertension Resource Pavilion will be open from 9:00 a.m. to 1:00 p.m. and from 3:00 to 5:15 p.m. Monday, May 3. High Tea and Poster Viewing will take place from 4:15 to 5:15 p.m. The ASH Hypertension Resource Pavilion will be the third floor of the Hilton.

The hall features many scientific, technical, periodical, and book exhibits designed to support hypertension specialists in providing the best care for their patients. This year, featured in the program book for a schedule of events.

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1 INDICATIONS AND USAGE

Benicar is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

2 CONTRAINDICATIONS

None.

3 WARNINGS AND PRECAUTIONS

1. Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. There have been reports of fetal and neonatal deaths in women who were taking angiotensin-converting enzyme (ACE) inhibitors. When ACE inhibitors were used for indications other than hypertension in patients with bilateral renal artery stenosis, oliguria and/or azotemia occasionally occurred. In such cases, these events may be related to angiotensin II dominance, even after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Early dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

2. Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin-aldosterone system, such as those who are salt-depleted (e.g., following the use of thiazide diuretics), symptomatic hypotension may be anticipated after initiation of treatment with Benicar. In these cases, saline should be administered before initiating the angiotensin II receptor antagonist. However, symptomatic hypotension does occur, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline.[See Dosage and Administration (2.1) in the full prescribing information]. A transient hypotensive response is not a contraindication to further treatment, which can usually be continued without difficulty even after the blood pressure has stabilized.

3. Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with Benicar. In patients whose renal function may be compromised, particularly those with renal artery stenosis, ACE inhibitors are generally contraindicated. There has been no long-term use of Benicar in patients with unilateral or bilateral renal artery stenosis. Therefore, results may be expected.

4. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.2 Post-Marketing Experience

The following adverse reactions have been reported in post-marketing experience with Benicar. These include reports of adverse reactions similar to those reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship between an adverse event and a drug.

7. DRUG INTERACTIONS

No significant drug interaction studies were reported in studies in which Benicar was co-administered with digoxin or warfarin in healthy volunteers.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C (1st trimester) and D (2nd and 3rd trimesters). In this clinical study with the use of Benicar in pregnant women[see Warnings and Precautions (5.1)].

8.3 Nursing Mother

Benicar is excreted in human milk, and it is not known whether it could affect a nursing infant. Because many drugs are excreted in human milk, caution should be exercised when Benicar is administered to a nursing mother.

8.4 Pediatric Use

The antihypertensive effects of Benicar were evaluated in a randomized, double-blind clinical study in pediatric patients 1 to 16 years of age (see Clinical Trials in the full prescribing information). The pharmacokinetics of Benicar were evaluated in pediatric patients 1 to 16 years of age (see Clinical Pharmacology (12.3) in the full prescribing information). Benicar was generally well tolerated in pediatric patients, and the adverse experience profile was similar to that described for adults.

8.5 Geriatric Use

The total number of hypertensive patients receiving Benicar in clinical studies, was more than 2500 patients/subjects, including more than 100 patients aged 65 years and older. No adverse reaction related to age was identified in these studies.

8.6 Hepatic Impairment

Increases in AUC, and Cmax were observed in patients with moderate hepatic impairment compared to those in matched controls, with an increase in AUC of about 60%. No initial dosage adjustment is recommended for patients with moderate hepatic dysfunction[see Dosage and Administration(2.1) and Clinical Pharmacology(12.3) in the full prescribing information].

8.7 Renal Impairment

Patients with renal insufficiency have elevated serum concentrations of olmesartan compared to subjects with normal renal function. After repeated dosing, the AUC was approximately 2-fold higher in patients with severe renal impairment (creatinine clearance <30 mL/min) when compared to patients with normal renal function (creatinine clearance greater than 90 mL/min).[See Dosage and Administration(2.1).]

8.8 Black Patients

The antihypertensive effect of Benicar was smaller in black patients (usually a low-renin population), as has been seen with ACE inhibitors, beta-blockers and other angiotensin receptor blockers.

10 OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia. Bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If hypotensive symptoms occur, initiate supportive treatment. The dialyzability of olmesartan medoxomil has not been determined.

16 STORAGE

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Manufactured for Daiichi Sankyo, Inc.

Parsippany, New Jersey 07054-0003

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BENICAR HCT Tablets (olmesartan medoxomil-hydrochlorothiazide)

Drial Summary – See package insert for full prescribing information.

USE IN PREGNANCY

When pregnancy is detected, discontinue Benicar as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.
**Hypertension in Women: Society for Women's Health Research**

Consistent with data from other clinical trials, the incidence of adverse experiences was greater in women than in men. There were relatively few patients with casual laboratory data that could be compared across gender. The following adverse experiences have been reported with olmesartan medoxomil and hydrochlorothiazide: a transient hypotensive response is not a contraindication to further treatment in hypertension.

**Renal and Hematologic Effects**

Thrombocytopenia has been reported with platelet counts at or below 10,000/mm³ in patients with severe hypertension. Renal impairment was not observed in patients with renal disease who received olmesartan medoxomil-hydrochlorothiazide. However, the possibility of renal impairment cannot be excluded. These effects may be due to a single cause or to independent phenomena (e.g., pancreatitis) do not occur with hydrochlorothiazide. Therapy with any combination of Olmesartan medoxomil and hydrochlorothiazide will be associated with increased BUN or creatinine.

**Therapeutic Uses**

The recommended dosage for Olmesartan medoxomil-hydrochlorothiazide is the same as for BENICAR and hydrochlorothiazide. The recommended starting dose of BENICAR HCT Tablets (olmesartan medoxomil-hydrochlorothiazide) for most patients is 40 mg/day.

**Drug Interactions**

Olmesartan medoxomil is not expected to interact significantly with theophylline and warfarin. The effect of olmesartan medoxomil on theophylline disposition has not been studied. Concomitant use of olmesartan medoxomil and warfarin resulted in no clinically meaningful changes in prothrombin time. Co-administration of olmesartan medoxomil and theophylline did not significantly alter the pharmacokinetics of theophylline.

**Special Populations**

**Patients with Renal Impairment**

BENICAR HCT tablets may be administered with other antihypertensive agents. Dosing should be individualized. Depending on the blood pressure response, the dose may be increased to 40 mg. Doses greater than 40 mg should be used with caution. If hypotensive response occurs, discontinued, the dose may be reduced to 20 mg. In cases of severe hypertension, 2-4 mg once daily is recommended. However, in cases of acute hypertension, 2-4 mg once daily is recommended. However, in cases of acute hypertension, 2-4 mg once daily is recommended.

**Pregnant Women**

Using infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Drug Metabolism**

Clinical studies of BENICAR HCT® (olmesartan medoxomil and hydrochlorothiazide) have not included sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be made cautiously, usually starting at the lower end of the recommended dosage range, and titrating upward as needed, with due consideration given to possible age-related changes in liver, renal, or cardiac function, and to presence of other concomitant diseases or other drugs that affect the patient's pharmacokinetics.

**Hepatic Impairment**

There are no studies of the effect of liver function impairment on olmesartan medoxomil and hydrochlorothiazide exposure. Therefore, the recommended regimen may need to be modified in patients with more severe hepatic impairment.
Figure 3: Probability of Achieving Systolic Blood Pressure (SBP)<140 mmHg at Week 8 With LOCF

Figure 4: Probability of Achieving Diastolic Blood Pressure (DBP) < 90 mmHg at Week 8 With LOCF
5.6 Patients with Impaired Renal Function

Azer. There are no studies in Azer in patients with renal impairment.

Olmesartan medoxomil. Changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil as a consequence of inhibiting the renin-angiotensin-aldosterone system. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria or progressive azotemia (and rarely) with acute renal failure and/or death. Similar effects may occur in patients treated with Azer because of the olmesartan medoxomil component (See Clinical Pharmacology (12.3) in the full prescribing information).

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar effects would be expected with olmesartan medoxomil and Azer.

5.7 Patients with Hepatic Impairment

Amlodipine. Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t1/2) is 58 hours in patients with severely impaired hepatic function, extreme caution when administering Azer to patients with severe hepatic impairment.

Patients with hepatic impairment have decreased clearance of amlodipine. Starting amlodipine or adding amlodipine at 2.5 mg in heparically impaired patients is recommended. The lowest dose of Azer is 5/20 mg; therefore, initial therapy with Azer is not recommended in heparically impaired patients (See Use in Specific Populations (8.6)).

5.8 Laboratory Tests

Azer. There was a greater decrease in hemoglobin and hematocrit in the combination product compared to either component. Other laboratory changes can usually be attributed to either monotherapy component.

5.9 Effects on Laboratory Tests

Amlodipine. In post-marketing experience, hepatic enzyme elevations have been reported (6.2).

Olmesartan medoxomil. In post-marketing experience, increased blood creatinine levels and hyperkalemia have been reported.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Azer

The data described below reflect exposure to Azer in more than 1600 patients including more than 1000 exposed for at least 6 months and more than 700 exposed for 1 year. Azer was studied in one placebo-controlled factorial trial (see Section 14.1 in the full prescribing information). The population had a mean age of 54 years and included approximately 55% males. Seventy-one percent were Caucasian and 25% were Black. Patients received doses ranging from 5/20 mg to 10/40 mg orally once daily.

The overall incidence of adverse reactions on therapy with Azer was generally mild and seldom led to discontinuation of treatment (2.6% for Azer and 6.8% for placebo). The reported adverse reactions were dose-related with placebo.

The adverse event profile obtained from 44 week of open-label combination therapy with amlodipine plus olmesartan medoxomil was similar to that observed during the 8-week, double-blind, placebo-controlled period.

The incidence ( % ) of dose-related side effects was as follows:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>2.5 mg</th>
<th>5.0 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-% (N=231)</td>
<td>1.2%</td>
<td>3.3%</td>
<td>6.2%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Female-% (N=334)</td>
<td>0.5%</td>
<td>1.4%</td>
<td>2.9%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

6.2 Post-Marketing Experience

The overall frequency of adverse events was not dose-related. Analysis of gender, age, and race groups demonstrated no differences between olmesartan medoxomil- and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e., 79/3278) of patients treated with olmesartan medoxomil and 2.7% (i.e., 210/7579) of control patients. In placebo-controlled trials, the only adverse event that occurred in more than 1% of patients treated with olmesartan medoxomil and at a higher incidence in olmesartan medoxomil treated patients vs. placebo was dizziness (3% vs 1%).

6.3 Laboratory Tests

Amlodipine. In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of Other Agents on Amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit Juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. Co-administration of the antacid Maalox® (antacid; Co-administration of the antacid Maalox® with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

In a single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

6.4 Pregnancy

Amlodipine. Amlodipine is not expected to cause fetal harm when administered to pregnant women. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

6.5 Nursing Mothers

Amlodipine. Amlodipine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when amlodipine is administered to a nursing woman.

6.6 Pediatric Use

Amlodipine. Studies of amlodipine in children and adolescents are not available.

6.7 Geriatric Use

Amlodipine. Elderly patients may be more sensitive to the effects of amlodipine. Studies have shown that elderly hypertensive patients treated with amlodipine had side effects similar to those observed in younger patients. Caution should be exercised when treating elderly hypertensive patients with amlodipine.

6.8 Use in Specific Populations

Amlodipine. The pharmacokinetics of amlodipine are not affected by age (74 to 213 years of age).

6.9 Overdose

Amlodipine. A single oral dose of 20 mg amlodipine was fatal in a 30-year-old man who had been drinking ethanol. The effects of acute and chronic amlodipine overdosage are unknown. Symptoms reported include lethargy, dizziness, light-headedness, syncope, hypotension, somnolence, apnea, convulsions, cardiac arrest, and death.

7 DRUG INTERACTIONS

7.1 Drug Interactions with Azer

The pharmacokinetics of amlodipine and olmesartan medoxomil are not altered when the drugs are co-administered.

No drug interaction studies have been conducted with Azer and other drugs, although studies have been conducted with the individual amlodipine and olmesartan medoxomil components of Azer, as described below, and no significant drug interactions have been observed.

7.2 Drug Interactions with Amlodipine

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of Other Agents on Amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit Juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

In a single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Effect of Amlodipine on Other Agents

Amlodipine: Amlodipine had no effect on the pharmacokinetics of digoxin, phenytoin, and indomethacin.

7.3 Drug Interactions with Olmesartan Medoxomil

No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan medoxomil was not significantly altered by the co-administration of antacids (Al(OH)3/Mg(OH)2).

Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes: Amlodipine. Co-administration of olmesartan medoxomil was well tolerated, with an incidence of adverse events similar to that seen with placebo. Events were generally mild, transient, and without relationship to the dose of olmesartan medoxomil.

The overall frequency of adverse events was not dose-related. Analysis of gender, age, and race groups demonstrated no differences between olmesartan medoxomil- and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e., 79/3278) of patients treated with olmesartan medoxomil and 2.7% (i.e., 210/7579) of control patients. In placebo-controlled trials, the only adverse event that occurred in more than 1% of patients treated with olmesartan medoxomil and at a higher incidence in olmesartan medoxomil treated patients vs. placebo was dizziness (3% vs 1%).
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Olmesartan medoxomil. Pregnancy Categories C (first trimester) and D (second and third trimesters). [See Warnings and Precautions (5.1)]

Amlodipine. No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the maximum recommended human dose of 10 mg amlodipine on a mg/m² basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg). However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout gestation. Amlodipine maleate has been shown to prolong both the gestational period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 lactation
The safety and effectiveness of Azor in pediatric patients have not been established.

Amlodipine. The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Olmesartan medoxomil. Safety and effectiveness of olmesartan medoxomil in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of subjects in the double-blind clinical study of Azor, 20% (384/1940) were 65 years of age or older and 3% (62/1940) were 75 years or older. No overall differences in safety or effectiveness were observed between subjects 65 years of age or older and younger subjects.

Elderly patients have decreased clearance of amlodipine. Starting amlodipine or adding amlodipine at 2.5 mg in patients ≥75 years old is recommended. The lowest dose of Azor is 5/20 mg; therefore, initial therapy with Azor is not recommended in patients ≥75 years old.

Amlodipine. Reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40% to 60%, and a lower initial dose may be required.

Olmesartan medoxomil. Of the total number of hypertensive patients receiving olmesartan medoxomil in clinical studies, more than 20% were 65 years of age and over. While more than 5% were 75 years of age and older, no overall differences in effectiveness or safety were observed between elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic impairment
There are no studies of Azor in patients with hepatic insufficiency, but both amlodipine and olmesartan medoxomil show moderate increases in exposure in patients with hepatic impairment. Use caution when administering Azor to patients with severe hepatic impairment.

Patients with hepatic impairment have decreased clearance of amlodipine. Starting amlodipine or adding amlodipine at 2.5 mg in patients with hepatic impairment is recommended. The lowest dose of Azor is 5/20 mg; therefore, initial therapy with Azor is not recommended in hepatically impaired patients.

8.7 Renal impairment
There are no studies of Azor in patients with renal impairment.

Amlodipine. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Olmesartan medoxomil. Patients with renal insufficiency have elevated serum concentrations of olmesartan compared with patients with normal renal function. After repeated dosing, AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 mL/min). No initial dosage adjustment is recommended for patients with moderate to marked renal impairment (creatinine clearance <40 mL/min).

8.8 Black patients
Of the total number of subjects in the double-blind clinical study of Azor, 25% (481/1940) were black patients. Azor was effective in treating black patients (usually a low-renin population), and the magnitude of blood pressure reduction in black patients approached that observed for non-black patients.

10 OVERDOSAGE
There is no information on overdosage with Azor in humans.

Amlodipine. Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m² basis) caused a marked peripheral vasodilatation and hypotension. Overdose might be expected to cause excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium-entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Olmesartan medoxomil. Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension should occur, supportive treatment should be initiated. The daliability of olmesartan is unknown.

17 PATIENT COUNSELING INFORMATION
Physicians should instruct female patients of childbearing age about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be informed to report pregnancies to their physicians as soon as possible. [See Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]
USE IN PREGNANCY
When pregnancy is detected, discontinue AZOR as soon as possible. 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. See WARNINGS AND PRECAUTIONS, Fetal/Neonatal Morbidity and Mortality.

Hypotension in Volume- or Salt-Depleted Patients
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients, symptomatic hypotension due particularly to the olmesartan component may occur after initiation of treatment with AZOR. Treatment should start under close medical supervision.

Vasodilation
Since the vasodilation attributable to amlodipine in AZOR is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering AZOR, particularly in patients with severe aortic stenosis.

Severe Obstructive Coronary Artery Disease
Patients, particularly those with severe obstructive coronary artery disease, may develop increased frequency, duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase.

Congestive Heart Failure
In general, calcium channel blockers should be used with caution in patients with heart failure.

Impaired Renal Function
In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar effects would be expected with AZOR because of the olmesartan medoxomil component.

Hepatic Impairment
Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with severely impaired hepatic function, caution should be exercised when administering AZOR to patients with severe hepatic impairment. Initial therapy with AZOR is not recommended in hepatically impaired patients.

Laboratory Tests
There was a greater decrease in hemoglobin and hematocrit in the combination product compared to either component alone.

Adverse Reactions
The only adverse reaction that occurred in greater than or equal to 3% of patients treated with AZOR and more frequently than placebo was edema. The placebo-subtracted incidence was 5.7% (5/20 mg), 6.2% (5/40 mg), 13.3% (10/20 mg), and 11.2% (10/40 mg). The edema incidence for placebo was 12.3%.

Adverse reactions seen at lower rates but at about the same or greater incidence as in patients receiving placebo included hypotension, orthostatic hypotension, rash, pruritus, palpitation, urinary frequency, and nocturia.

In individual clinical trials of amlodipine and olmesartan medoxomil, other commonly reported adverse reactions included headache, dizziness, and flushing.

Geriatric Use
Elderly patients have decreased clearance of amlodipine. Initial therapy with AZOR is not recommended in patients ≥75 years old.

Please see full prescribing information for AZOR.
AZOR is indicated for the treatment of hypertension, alone or with other antihypertensive agents. AZOR is indicated as initial therapy in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals. Initial therapy with AZOR is not recommended in patients ≥75 years of age or in hepatically impaired patients.

BENICAR® (olmesartan medoxomil) and BENICAR HCT (olmesartan medoxomil-hydrochlorothiazide) 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 inside back cover for important safety information for BENICAR and BENICAR HCT.

For more information, please visit www.AZOR.com
Please see preceding page for important safety information.
Please see brief summary of prescribing information for AZOR, including boxed WARNING regarding avoiding use in Pregnancy.
**WARNING: AVOID USE IN PREGNANCY**
When pregnancy is detected, discontinue BENICAR or BENICAR HCT as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

**Hypotension in Volume- or Salt-Depleted Patients**
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with BENICAR. Treatment should start under close medical supervision. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

**Impaired Renal Function**
In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

**The prescribing information for BENICAR HCT also includes the following warnings regarding its hydrochlorothiazide component:**
- 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

**Fetal/Neonatal Morbidity and Mortality**
Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

**Hepatic Impairment**
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

**Hypersensitivity Reaction**
Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

**Systemic Lupus Erythematosus**
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

**Lithium Interaction**
Lithium generally should not be given with thiazides.

**Adverse events**
- 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% vs 0%), hyperuricemia (4% vs 2%), dizziness (9% vs 2%), and upper respiratory tract infection (7% vs 0%)

**Dosing and administration**
- No initial dosage adjustments are recommended 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
- For BENICAR HCT, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range

*Creatinine clearance <40 mL/min.

Please see full prescribing information for BENICAR and BENICAR HCT.
WARNING: AVOID USE IN PREGNANCY
When pregnancy is detected, discontinue BENICAR or BENICAR HCT as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

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.

For more information, please visit www.BENICAR.com

Please see preceding page for important safety information.

Please see brief summary of prescribing information for BENICAR and BENICAR HCT, including boxed WARNING regarding avoiding use in Pregnancy.