Renowned cardiologist to review the history of hypertension, look at what’s on the horizon for the field

Eugene Braunwald, MD, says it’s important for researchers and clinicians to understand how medicine has evolved.

Research in any field — especially medicine — is a dynamic process, and renowned Harvard cardiologist Eugene Braunwald, MD, said he believes scientists can do better work with greater inspiration if they understand the grand achievements and great frustrations of past research efforts.

Dr. Braunwald will present the keynote address ‘Hypertension: The Past — The Present — The Future’ during Plenary Session 1, which takes place from 12:00 to 3:10 p.m. on Sunday, May 2, in the East Ballroom. Dr. Braunwald’s lecture will begin at 1:00 p.m.

“This is a hundred-thousand-foot view of the entire field,” Dr. Braunwald said. “As a cardiologist, I consider myself a first cousin to the hypertension specialist. As a close cousin, I would like to share with the group what I believe to be terribly important about this field.”

Dr. Braunwald, who is the Distinguished Hersey Professor of Medicine at Harvard Medical School, will begin in 2760 BC with a Chinese emperor who described a “strong, forceful pulse” in a medical textbook.

“This is probably the first description of hypertension,” he said.

From there, Dr. Braunwald will trace the development of the understanding of hypertension — from the 19th century, before good methods for measuring blood pressure were developed, through the turn of the 20th century and the invention of the blood pressure cuff and the stethoscope.

“The largest portion of my lecture is the past,” he said. “These attendees know about the present… I consider medicine to be a learned profession. If you’re in a learned profession, you need to appreciate where you came from and how you fit in to something much larger. “I think very often we get caught up in medicine in looking at the leaves — people say you don’t want to miss the forest for the trees. I think many times we’re not even looking at the trees. We’re looking at the leaves of the trees, and we’re missing the trees, and obviously if you miss the trees, you miss the forest.”

“I think it’s important — especially if you’re doing research — to be inspired by the achievements and the frustrations of the people who went before us and marvel at how smart they were with so little information.”

“I think it’s important — especially if you’re doing research — to be inspired by the achievements and the frustrations of the people who went before us and marvel at how smart they were with so little information.”
Program dedicated to educating clinicians, scientists on the latest developments in the field

For attendees looking for a thorough examination of the timeliest issues in the field of hypertension, be sure to attend the Hypertension Highlights program from 8:00 a.m. to 3:00 p.m., Saturday, May 1, in the Hypertension Highlights Ballroom.

Hypertension Highlights is a daylong program dedicated to educating clinicians and scientists about some of the most interesting, controversial, and evolving topics in the field. The program includes state-of-the-art presentations on current and emerging aspects of hypertension, including mechanisms, and the management of special populations.

Hypertension Highlights, which is held in association with the New York State Chapter of the American College of Cardiology, is an ideal update for hypertension specialists and those wishing to become specialists in the field.

PART I

Part I of Hypertension Highlights will include four 30-minute lectures on topics from the sympathetic nervous system’s role in blood pressure regulation to gender differences in hypertension.

Co-chair Shawna D. Nesbitt, MD, MS, who is Associate Professor of Medicine at the University of Texas Southwestern Medical Center, said the information being presented is interesting because it will help scientists and clinicians alike better understand the underlying mechanisms behind hypertension, which, in turn, leads to better treatment.

“As we begin to understand the mechanisms better, we are better equipped to take care of patients,” she said. “We tend to focus a lot on drugs, but if we don’t understand the mechanisms behind the cause of hypertension to begin with — then just lowering blood pressure is meaningless to some extent. We may not actually make any difference in the long run, and to some extent, we may be harming people.”

To begin Part I, Allyn L. Mark, MD, will present ‘Decreased Activity in Obesity and Hypertension: What’s Behind It and What Can We Do About It?’

Dr. Mark’s work has focused on understanding the origin of the sympathetic nervous system and how it actually propagates the elevation of blood pressure and how it changes over time,” said Dr. Nesbitt. “The implications of his work help us get more insight into treatment and retrospectively understand the origination of the blood pressure elevation from the start.”

Clyde W. Yancy, MD, will then provide an “Update on the Evaluation and Treatment of Heart Failure.”

“Dr. Yancy is a leader in the field of heart failure and it’s a very nice fit to have him follow Dr. Mark,” Dr. Nesbitt said. “Dr. Yancy did some work with carvedilol and looked at the sympathetic nervous system and drugs that affect that system and heart failure. His work helps us understand the role carvedilol plays in helping some of the sympathetic nervous system in heart failure patients. He’s likely to discuss what treatments we should be changing now.”

Dr. Nesbitt said Dr. Yancy will also likely discuss blood pressure goals for heart failure patients in light of the ACCORD data.

“Whether that has any affect on heart failure patients at all will be an interesting question,” she said.

The next two talks — ‘The Impact of Sex on Blood Pressure and Hypertension’ by Kathryn Sandberg, PhD, and ‘Update on Cardiovascular Health In Women’ by Martha Gulati, MD, MS — also tie together nicely, Dr. Nesbitt said. “Always keep in mind that there are differing factors and it’s especially regarding heart disease and hypertension,” she said.

“Looking at that differing appearance of blood pressure elevation and of cardiovascular disease is important because we should treat people individually. We need to look at the data as it relates to women — particularly as the numbers change. We’re seeing a larger predominance of elderly in the population overall, and women outlive men, so we’ll be treating more older women. Understand how to take care of older women will be an important part of cardiovascular care going forward.”

PART II

Allyn L. Mark, MD, who is Professor of Medicine at State University of New York Downstate Medical Center College of Medicine, will moderate a panel discussion during Part II of the Hypertension Highlights program.

“This year we’ve urgently needed a detailed discussion about identifying the unmet needs in the care of hypertension in the United States right now,” Dr. Weber said. “Do we need more drugs? Do we need more lifestyle modification? Do we need more education of patients or these anything we can do about the fact that our population is getting more obese? Are we putting too much emphasis on superficial solutions rather than dealing with the core problems? What can we do about the fact that we have an aging population? Whether or not they have other things going on, as people age, they are much more likely to have hypertension and the consequences of hypertension, including heart failure, stroke, and kidney disease. What are the unmet needs there?”

Dr. Weber said he hopes the panel, which is made up of experts in the fields of aging, diabetes, heart disease, and renal disease, will address these questions and other concerns facing the profession and the nation.

PART III

Following lunch, a trio of 30-minute lectures will take place during Part III of the program. Co-chair Raymond R. Townsend, MD, Professor of Medicine at the University of Pennsylvania, said Part III will cover the nuts and bolts of daily care.

Bertram Pitt, MD, will kick off the afternoon with his talk ‘Electrolyte Disturbances in Hypertension Management.’

During the second talk, ‘Update in Pathophysiology and Therapy of Renal Vascular Hypertension,’ Lilach O. Lerman, MD, PhD, and Steven C. Textor, MD, will review results from the large United Kingdom study ASTRAL (Angioplasty and Stenting for Renal Artery Lesions).

ASTRAL sought to determine if renal arterial revascularization with balloon angioplasty and/or endovascular stenting can safely prevent progressive renal failure among a wide range of patients with atherosclerotic renovascular disease, and the results have been somewhat controversial — suggesting that angioplasty and/or stenting may not always be beneficial, and in some cases may cause harm, Dr. Townsend said.

“It begs the question ‘do I fix or not?’” he said. “Intervention may improve things or may cause harm. ASTRAL suggests we don’t know when intervention is the right choice.”

Dr. Townsend said Dr. Textor is on the cutting edge in this area and his work with BOLD (blood-oxygen level dependent) MRI may help determine who might benefit from angioplasty or stenting.

During the final talk, “Update: Biomarkers as a Tool to Assess Renal Risk and Renal Injury,” presenter Brad C. Astor, PhD, MPH, will address a hot topic with tremendous opportunity to improve diagnostic approaches in hypertension.

Hypertension Highlights 2010

Part I

8:00 – 8:30 A.M. The Symptomatic Nervous System in Hypertension

Allyn L. Mark, MD

8:30 – 9:00 A.M. Update on the Evaluation and Treatment of Heart Failure

9:00 – 9:30 A.M. Gender Difference in Hypertension

Kathryn Sandberg, PhD

9:30 – 10:00 A.M. Update on Cardiovascular Health in Women

Martha Gulati, MD, MS

10:00 – 10:30 A.M. Break

10:30 – 11:00 A.M. Integrated Guidelines: Metabolic Syndrome, Where are We Going?

James R. Sowers, MD

Part II

11:00 A.M. – 11:15 A.M. Panel Discussion: Goals of Blood Pressure Reduction

Michael A. Weber, MD, Moderator

Atul R. Chugh, MD, Age

William C. Cushman, MD, Diabetes

Sriraj Bangalore, MD, Heart Disease

Abdi. J. Dasko, MD, Renal Disease

11:15 – 12:15 P.M. Lunch

Part III

1:30 – 2:00 P.M. Electrolyte Disturbances in Hypertension Management

Bertram Pitt, MD

2:00 – 2:30 P.M. Update in Pathophysiology and Therapy of Renal Vascular Hypertension

Lilach O. Lerman, MD, PhD and Steven C. Textor, MD

2:30 – 3:00 P.M. Update: Bio Markers as a Tool to Assess Renal Risk and Renal Injury

Brad C. Astor, PhD, MPH

Welcome, continued from page 1

opportunities to discuss and explore the increasing scrutiny surrounding the relationships between academic physicians and industry.

Beginning at 3:30 p.m. on Saturday, May 1, Michael A. Weber, MD, will join Dr. Black in moderating a session that will examine the reasons for recent criticism of these relationships, discuss the meaning of conflict of interest, and ask if academic physicians have become too dependent on industry. See story, page 3.

At 9:00 a.m. on Monday, May 3, P. Roy Vagelos, MD, will also discuss “Academic Industry Relations” as part of a Translational Track session.

As always, the plenary sessions are sure to be a highlight, and Dr. Black said he is pleased that renowned cardiologist Eugene Braunwald, MD, will present the keynote address ‘Hypertension: The Past — The Present — The Future’ during Plenary Session I, which takes place at noon on Sunday, May 2.

In addition to the exciting plenary lectures, Dr. Black said he is glad the “What the Hypertension Specialist Should Know” series continues this year. The annual meeting will also include collaborative sessions with several specialty organizations that will examine common issues and provide attendees with opportunities to expand their knowledge and foster new relationships.

This year, ASH is working with many organizations, including the New York State Chapter of the American College of Cardiology, the American Heart Association Council for High Blood Pressure Research, the Consortium for Southeastern Hypertension Control, the European Society of Hypertension, and many more.

“Our partnerships with other organizations that share similar interests are quite important to our Society and to our annual meeting,” Dr. Black said. “Our meeting is the most important thing that we do. It is a place for exchanging ideas and networking — not only about blood pressure but also about global risk and related diseases. So it’s important we broaden our horizons and collaborate with our peers in the United States and worldwide.”
Sessions will explore the working relationships between clinicians, corporations and industry.

For many decades, medical progress has largely been the result of collaboration between academic physicians and industry. The medical industry relies on academic physicians to identify unmet needs in the community and to help define the kinds of devices, drugs, and tests that might be valuable. However, this relationship between academic physicians and industry has received increasing criticism in recent years. To examine these criticisms and the reasons behind them, a session on Physician-Industry Relations will take place from 3:30 to 4:30 p.m. Saturday, May 1, in Beekman Parlor.

ASH President Henry R. Black, MD, along with ASH past-President Michael A. Weber, MD, will moderate a series of talks as part of the special session. "This is a logical and longstanding relationship," Dr. Weber said. "It's come under criticism in recent years largely for financial reasons, because many people who operate health plans, including government agencies, are concerned that a number of new products and devices tend to be more expensive than what was previously available and therefore keep adding to the cost of health care. "And as much as everyone likes progress, they're asking, 'is there too much progress?'" So critics attempt to weaken the relationship between academic physicians and industry by talking about conflicts of interests or other issues, Dr. Weber said, potentially impairing the development of new therapies.

Speaker Thomas P. Stossel, MD, will delve more extensively into the reasons behind the criticism during his presentation "The Physician/Industry Relationship: Why is it Under Attack?" Dr. Stossel, a renowned oncologist and professor of Medicine at Harvard Medical School, is an outspoken advocate in defending physicians' ties to industry. The second speaker of the afternoon, Lance K. Stell, PhD, who is a professor of Philosophy and Director of Medical Humanities at Davidson College, will explore the meaning of "conflict of interest" and whether the relationships between physicians and corporations actually constitute a conflict. "There's no question that there should be guidelines and ethical standards to define the relationship between physicians and industry," Dr. Weber said. "We all know the importance of making the relationship between the physician and the industrial entity as transparent as possible, and I think we've been reasonably good about doing that."

He said there are some things that perhaps physicians shouldn't do, or should do with caution. However, Dr. Weber said physicians are the obvious choice for providing medical education to other physicians about new products.

"On the other hand, when physicians are presenting new information, they should be free to present it in an open and well-balanced fashion — to present it with their own interpretations and their own perspectives and not be beholden to the pharmaceutical industry or device industry or laboratory testing industry," he said. "It's the role of doctors to explain things, to interpret them; to point out what's weak as well as what's strong; to give credibility to data around new products."

Renowned endocrinologist and diabetes specialist Jeffrey R. Garber, MD, of the Division of Endocrinology, Harvard Vanguard Medical Associates, will give the final presentation "Are Academic Physicians, Individually and as Organizations, Too Dependent on Industry?"

I n an effort to strengthen relationships and the sharing of ideas and knowledge, the American Society of Hypertension has begun collaborating with the Sociedad Argentina de Hipertension Arterial (SAHA).

Saturday’s collaboration, the SAHA will present a joint symposium with ASH on Saturday, May 1, as part of the 25th ASH Annual Scientific Meeting. In addition, a second joint symposium will be presented at SAHA’s 2011 Congress in Argentina.

The symposium, entitled "Cardio-Metabolic Abnormalities in Arterial Hypertension," will take place from 3:30 to 4:30 p.m. in Beekman Parlor.

SAHA Vice President Roberto A. Ingaramo, MD, said he sought out ASH President Henry R. Black, MD, during the 2009 annual meeting in San Francisco to discuss the possibility of collaboration between the two groups.

“I wanted to try to strengthen the relations between our societies,” Dr. Ingaramo said. “I intend to give great importance to these upcoming joint symposia to continue a cycle that we hope will endure and to encourage scientific cooperation between both societies.”

Saturday’s joint symposium will provide an update on the structural cardiac changes and metabolic abnormalities most frequently found in hypertensive patients.

Thursday's joint symposium will provide an update on the structural cardiac changes and metabolic abnormalities most frequently found in hypertensive patients:

The symposium will include talks on "Diastolic Heart Failure and Hypertension," "Obesity and the Metabolic Syndrome: Cardiovascular and Renal Consequences," and "Statins and Lipids in Hypertension and Renal Disease.

We have several renowned speakers who will address these highly topical issues and will present recent data about the pathophysiology of these diseases and their influence on hypertension," Dr. Ingaramo said. In addition to learning the latest data, Dr. Ingaramo said he expects attendees to come away with practical information as well.

He will then look toward the future and discuss promising treatments for resistant hypertension, including electrical stimulation and the potential of endothelin blockers. However, his discussion of future advances will primarily focus on genetics. Dr. Braunwald will summarize what has been learned about genetics and hypertension thus far and examine how genetics may be used to prevent hypertension one day. "That is the pot of gold at the end of the rainbow," he said.
Winner to be honored Monday

Each year, the ASH Young Scholars Award recognizes the achievements of outstanding young investigators in the field of hypertension. The award will be presented during the Plenary Session II, which takes place from 1:15 to 4:15 p.m. on Monday, May 3, in the East Ballroom.

Bina Joe, PhD

Dr. Joe’s research focuses on the genetics of hypertension. Her research is funded through multiple grants from the National Heart Lung and Blood Institute. She works predominantly with the Dahl salt-sensitive and Dahl salt-resistant rats that were bred at her institution by her predecessor. Through sustained substitution mapping, research in Dr. Joe’s laboratory has marked improved resolutions required for the identification of multiple genomic loci linked to hypertension. By combining transcriptions with substitution mapping, Dr. Joe’s laboratory has prioritized candidate genes that were previously not implicated in hypertension. Her most recent work has identified that variants of a gene linked to hypertension in rats is also genetically associated with human essential hypertension. Dr. Joe has served as an adhoc member of several NIH study sections since 2005. She has also served as an international reviewer for the Medical Research Council of UK and the WELLCOME trust. She is a member of the editorial boards of Hypertension and Physiological Genomics.

Joint session to examine changing ideas about blood pressure regulation

During a joint session with the American Heart Association Council for High Blood Pressure Research, four experts will present insights into new paradigms in the field of hypertension. The session, “Molecular Mechanisms of Hypertension: Novel Concepts and Clinical Implications,” will take place from 3:30 to 5:00 p.m. on Saturday, May 1, in Sutton Center.

“This is going to be a very interesting session because we’re going to learn about some new concepts related to hypertension both at the basic science and the clinical levels. Factors that previously would never have been considered to be implicated in blood pressure regulation, such as the immune system and adipose tissue, are now emerging to be important in the pathogenesis of hypertension,” said session chair Rhian M. Touyz, MD, PhD, who is a senior scientist at the Ottawa Hospital Research Institute in Ontario.

The session will open with two presentations on molecular mechanisms of hypertension. Dominik N. Müller, MD, will talk about the immune system and inflammation and what this means in terms of hypertension. Lisa Cassis, PhD, will discuss the role of adipose tissue and the renin angiotensin system in relation to hypertension.

“We will then switch to the clinical arena where we have two excellent clinician scientists. Anna F. Dominiczak, MD, will explore an integrative understanding of the mechanisms of clinical hypertension and how sophisticated new technologies like genomics, proteomics, and metabolomics can help in understanding complex diseases, like hypertension,” Dr. Touyz said. “Thomas M. Coffman, MD, will close the session by discussing hypertension as a multi-system disease involving the kidneys, the heart, and the vessels.”

Session Highlights

The “Molecular Mechanisms of Hypertension: Novel Concepts and Clinical Implications” session held in partnership with the American Heart Association Council for High Blood Pressure Research (HBPR) will take place from 3:30 to 5:00 p.m. in Sutton Center.

10:30 A.M.
RAS, Inflammation and Immunity: Implications in Hypertension
Dominik N. Müller, MD, Berlin, Germany

11:30 A.M.
Adipocytes and Vascular Cell Networking: A Link Between Obesity and Hypertension
Lisa A. Cassis, PhD, Lexington, KY

1:15 P.M.
Systems Medicine Strategies in Cardiovascular Prevention
Anna F. Dominiczak, MD, Glasgow, United Kingdom

4:30 P.M.
The Kidneys, the Heart and the Vessels in Clinical Hypertension: Lessons from Mice
Thomas M. Coffman, MD, Durham, NC

Meet the Expert Sessions

Meet the Expert sessions provide an opportunity for interaction and consultation with professionals who have expertise in a specific area. Attendees will be admitted on a first-come, first-served basis.

Sunday, May 2

10:00 – 11:00 A.M.
Updates and Results on Women’s Health Initiative
Karen L. Mergler, MD, MPH, Minneapolis, MN
Morgan Suite

Management of Low HDL
Cholesterol
Howard Weintraud, MD, New York, NY
Bryant Suite

Isolated Systolic Hypertension
John B. Koetis, MD, New Brunswick, NJ
Clinton Suite

How to Interpret a Clinical Trial Manuscript
Richard R. Greiner, MD, PhD, Minneapolis, MN
Bryant Suite

Hypertension and Air Pollution
Robert D. Brook, MD, Axon Ahrn, MD
Gibson Suite

11:45 – 1:45 P.M.
Angiotensin 1-7: Is it Relevant?
Carolee Ferrante, MD, Winston-Salem, NC
Sutton North

Pharmacokinetics, Pharmacodynamics and Drug Interaction
Dominic A. Sica, MD, Richmond, VA
Morgan Suite

Vascular Function
Raymond R. Townsend, MD, Philadelphia, PA
Bryant Suite

Imaging for Secondary Causes of Hypertension
Thomas A. Sos, MD, New York, NY
Clinton Suite

Peripheral Vascular Disease
Kawar Singh, MD, Farmington, CT
Gibson Suite

Monday, May 3

11:45 A.M. – 12:45 P.M.
Renal Sympathetic Nerves
Gerald P. Dibernano, MD, Iowa City, IA
Bryant Suite

The Treatment of Atrial Fibrillation in the Hypertensive Patient
Peter R. Kowey, MD, Wynnewood, PA
Gibbon Suite

Metabolic Syndrome and Polycystic Ovary Syndrome
David A. Ehrmann, MD, Chicago, IL
Sutton North

Exercise Testing
Martha Golden, MD, Chicago, IL
Morgan Suite

ASH Corporate Members
Boehringer Ingelheim Pharmaceuticals, Inc.
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Forest Laboratories, Inc.
GlaxoSmithKline Pharmaceuticals
Merck & Co., Inc.
Nicox SA
Novartis Pharmaceuticals Corporation
Pfizer, Inc.
Takeda Pharmaceuticals North America, Inc.

Competitors to make presentations Saturday

The five finalists for the ASH Young Investigator-in-Training abstract competition will give their oral presentations from 9:00 to 5:00 p.m. on Saturday, May 1, in Rendezvous Trianon.

Each competitor is either a graduate student (medical, nursing, physician assistant, or pharmacy) a postdoctoral fellow, or a resident who is the first author of one or more abstracts accepted for presentation at the annual meeting.

The chosen finalists represent a wide range of investigational studies.

Carlos L. Alviar, MD, from St. Luke’s-Roosevelt Hospital Center and Columbia University College of Physicians and Surgeons, will present an abstract titled “Efficacy and Safety of Dual Calcium Channel Blocker (CCB) Therapy.”

Dr. Alviar said he was inspired to examine the safety and efficacy of CCB therapy after seeing patients in the hypertension clinic with Dr. Franz Meserli treating calcium channel blockers in combination despite limited evidence for such a strategy.

“We decided to do a literature review and found we had a good number of papers and clinical trials to do a meta-analysis,” he said.

Dr. Alviar said he found dual CCB therapy to be effective for blood pressure reduction and to be safe in terms of side effects during short-term follow up, because used in combination, dihydropyridines and non-dihydropyridines have a synergistic effect and usually require lower doses or exert a counteracting effect in terms of adverse effects.

“We consider that this combination could be an option for patients with resistant hypertension,” he said. “However these results have to be interpreted with caution as none of the trials had a long-term follow up, so mortality data or long-term side effects can not be estimated. Nonetheless blood pressure, which was the main endpoint assessed, was positively impacted.”

Maria Czarina Acelajado, MD, of the University of Alabama at Birmingham, will present another abstract, “Refractory Hypertension: Definition, Prevalence and Patient Characteristics.”

“Refractory hypertension is not really an accepted term yet, but we believe there is a distinct subgroup that needs to be categorized, which is what we’re trying to do,” Dr. Acelajado said.

The abstract she submitted is a retrospective study. She looked at a database of patients from 2004 to 2009 to evaluate several characteristics to determine if there are common links among patients who were unable to achieve blood pressure control.

“Our patient population is made of people who are referred to our hypertension clinic for difficulty controlling their blood pressure,” Dr. Acelajado said. “They have needed more than three medications to attempt to control their blood pressure. After six months, or at least three visits, we looked to see if we were successful in getting their blood pressure under control. We found a 15 percent incidence of refractory hypertension in our 280 patients.

“Among those patients, we found several things that set them apart from the patients we were able to control. These patients had a significantly higher number of antihypertensive medications at the 6-month follow-up compared to controlled patients. They had a higher baseline systolic blood pressure. They had a higher 24-hour urinary aldosterone level, and they also had a higher baseline heart rate.”

Young Investigator Finalists

Carlos L. Alviar, MD — St. Luke’s-Roosevelt Hospital Center and Columbia University College of Physicians and Surgeons

Maria Czarina Acelajado, MD — University of Alabama at Birmingham

Camilla Auferg, MD — Copenhagen University Hospital Glostrup

Kathirvel Gopalakrishnan, PhD — University of Toledo College of Medicine

Idda Z. Ben-Dov, MD, PhD — The Rockefeller University

2010 ASH Hypertension Community Outreach

For the third consecutive year, ASH offers its Hypertension Community Outreach Initiative in conjunction with the Annual Scientific Meeting and Exhibition. This program, which began in New Orleans in 2008, offers free health screenings for at-risk populations. For 2010, the outreach initiative provided hypertension screenings and education for local underserved and uninsured people at three screenings in the week leading up to the annual meeting.

“We are extremely proud of the continuing success and impact our outreach programs have had on large numbers of people including in low-access communities in New Orleans, San Francisco, and now in New York,” said Dr. Keith C. Ferdinand, leader of the American Society of Hypertension Community Outreach Program. “Studies demonstrate that a broad public health approach – with contributions from the community, medical experts, industry leaders and government officials – is essential to make a significant impact on high blood pressure across various populations, especially for those in need.”

ASH Director of Hypertension Community Outreach Services Gilda C. Caputo-Hansen said she is especially pleased that for 2010 the Society was able to greatly improve the education provided during outreach events thanks to the recent publication of a new educational brochure “Blood Pressure and Your Health.”

The brochure, which is available in English and Spanish, has been very helpful in explaining hypertension to patients at health screenings. Previously, people didn’t understand what hypertension was; what it meant for their health.

Now, thanks to a grant and a lot of hard work by ASH and HealthEd, the patient education agency that assisted in producing the brochure, patients come away with all the information they need to understand hypertension.

“During these follow ups, ASH will have Outreach Services booth, volunteer clinicians will offer free blood pressure screenings to attendees.”

Thank You to our Community Outreach Sponsors

Forest Pharmaceuticals, Inc.

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Product Showcase

Come see the Evolution of BP...
Resource Pavilion Opens Saturday

Don’t miss the opening day of the ASH Hypertension Resource Pavilion Saturday, May 1. The Resource Pavilion will be open from 3:00 to 7:00 p.m. Saturday. It can be found in Americas Hall on 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. Be sure to be there for the Opening Reception, which begins at 5:00 p.m. Saturday. Be sure to be there for the Opening Reception, which begins at 5:00 p.m. Saturday.

This year, featured in the Resource Pavilion Saturday, May 1. The Resource Pavilion will be open from 3:00 to 7:00 p.m. Saturday. It can be found in Americas Hall on the third floor of the Hilton.
A Cross-Examination of Contemporary Issues in Hypertension:

Join us for a unique and interactive CME dinner symposium

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.

Chair
George L. Bakris, MD
Professor of Medicine
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
Farmington, CT

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

Please join us for what promises to be a unique educational experience and earn 1.5 AMA PRA Category 1 Credits™

Please plan to arrive early to ensure seating

Please register on-site at 7:00 PM


**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 Pharmacology (12.3) in the full prescribing information). The pharmacokinetics of Benicar were evaluated in pediatric patients 1 to 16 years of age (see Clinical Pharmacology (12.4) 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, more than 20% were 65 years of age and older. With more than 5% were 75 years 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.

**17.2 Storage**

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

**18.2 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.

**18. OVERDOSAGE**

Limited data are available related to overdose in humans. The most likely manifestations of overdose would be hypotension and tachycardia; bronchospasm could be encountered if para sympathetic (vagal) stimulation occurs. If hypotensive effects occur, initiate supportive treatment. The dialyzability of olmesartan medoxomil is unknown.

**19. CLINICAL PHARMACOLOGY**

**19.1 Pharmacokinetics**

The bioavailability of olmesartan was not significantly altered by food. The following adverse reactions have been reported in postmarketing experience. Because these reactions are reported voluntarily from a large population of drug-treated patients, it is not possible to reliably estimate their frequency or to establish a causal relationship to drug exposure. Significant changes in standard laboratory parameters were rarely observed. Changes in renal function may be anticipated in susceptible individuals treated with Benicar. In patients whose renal function was limited to 30-60 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 0.4 mL/min/1.73 m². In patients whose renal function was limited to 15-30 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 1.0 mL/min/1.73 m². In patients whose renal function was limited to 10-15 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 2.0 mL/min/1.73 m². In patients whose renal function was limited to 5-10 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 2.5 mL/min/1.73 m². In patients whose renal function was limited to 0-5 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 3.0 mL/min/1.73 m².

**19.2 Animal Toxicology**

The antihypertensive response of olmesartan has been observed in studies conducted in normotensive and hypertensive rats. Because of the potential for adverse effects on the maternal and fetal renin-angiotensin system, changes in renal function may be anticipated in susceptible individuals treated with Benicar. In patients whose renal function was limited to 30-60 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 0.4 mL/min/1.73 m². In patients whose renal function was limited to 15-30 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 1.0 mL/min/1.73 m². In patients whose renal function was limited to 10-15 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 2.0 mL/min/1.73 m². In patients whose renal function was limited to 5-10 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 2.5 mL/min/1.73 m². In patients whose renal function was limited to 0-5 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 3.0 mL/min/1.73 m².

**19.3 Human Toxicology**

The antihypertensive response of olmesartan has been observed in studies conducted in normotensive and hypertensive rats. Because of the potential for adverse effects on the maternal and fetal renin-angiotensin system, changes in renal function may be anticipated in susceptible individuals treated with Benicar. In patients whose renal function was limited to 30-60 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 0.4 mL/min/1.73 m². In patients whose renal function was limited to 15-30 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 1.0 mL/min/1.73 m². In patients whose renal function was limited to 10-15 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 2.0 mL/min/1.73 m². In patients whose renal function was limited to 5-10 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 2.5 mL/min/1.73 m². In patients whose renal function was limited to 0-5 mL/min/1.73 m², the mean decrease in creatinine clearance was approximately 3.0 mL/min/1.73 m².
BENICAR HCT Tablets (olmesartan medoxomil-hydrochlorothiazide)

**Hypotension in Patients with an Activated Renin-Angiotensin System**

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those treated with high levels of diuretics), symptomatic hypotension may occur following the initial dose of BENICAR HCT®. Therefore, when olmesartan medoxomil-hydrochlorothiazide tablets and other antihypertensive agents are used concomitantly, the patients should be observed closely for hypotension. If symptomatic hypotension occurs, it may require treatment with volume expansion and/or adjustment of benzocaine (methopyrilene) dosage up to 30 mg nightly.

**Diabetic Retinopathy**

While the effect of olmesartan medoxomil-hydrochlorothiazide on the risk of diabetic retinopathy in patients with diabetes mellitus has not been studied in clinical trials, olmesartan medoxomil has been shown to reduce the risk of diabetic retinopathy in clinical trials involving diabetic patients treated with olmesartan medoxomil. Therefore, BENICAR HCT® should be used with caution in diabetic patients.

**Hepatitis C Virus Infection**

The use of olmesartan medoxomil-hydrochlorothiazide in patients with hepatitis C virus (HCV) infection has not been evaluated in clinical trials.

**Liver Function Tests**

Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be performed in all patients treated with BENICAR HCT®. In addition, periodic laboratory evaluations, including serum potassium, sodium, chloride, carbon dioxide, creatinine, uric acid, and blood urea nitrogen should be performed in patients who are candidates for the concomitant administration of potassium-sparing diuretics. If hyperkalemia occurs, dosage adjustment of the antidiabetic drug may be necessary.

**Hyperkalemia**

Hyperkalemia may also occur in patients taking other diuretics. If concomitant usage is required, specific potassium monitoring should be carried out, especially in the early stages of therapy. If hyperkalemia occurs, dosage adjustment of the antidiabetic drug may be necessary.

**Hypokalemia**

Hypokalemia may be expected in patients taking other diuretics. If concomitant usage is required, specific potassium monitoring should be carried out, especially in the early stages of therapy. If hypokalemia occurs, dosage adjustment of the antidiabetic drug may be necessary.

**Gender**

There is no evidence of therapeutic inequivalence in men and women (see CLINICAL PHARMACOLOGY, Special Populations). Special consideration should be given in selecting the initial drug(s) and dose(s) of treatment for patients with severe congestive heart failure, including those patients who have been receiving a diuretic, digoxin, and/or an ACE inhibitor. The titration of the diuretic should be made more gradual in these patients and the patient should be observed closely for hypokalemia and hypotension. In patients with severe congestive heart failure, maintenance doses of olmesartan medoxomil-hydrochlorothiazide tablets should be reduced or omitted for several days prior to the initiation of diuretic therapy. In patients with mild to moderate renal impairment (creatinine clearance >30 mL/min), the dosage of olmesartan medoxomil-hydrochlorothiazide tablets should be reduced as follows:

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Olmesartan Medoxomil</th>
<th>Hydrochlorothiazide</th>
<th>Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>20 mg</td>
<td>12.5 mg</td>
<td>32.5 mg</td>
</tr>
<tr>
<td>15-30</td>
<td>20 mg</td>
<td>12.5 mg</td>
<td>32.5 mg</td>
</tr>
<tr>
<td>≤15</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Special Populations**

**Pediatric Use**

The safety and effectiveness of olmesartan medoxomil-hydrochlorothiazide tablets in children have not been established. Therefore, the use of olmesartan medoxomil-hydrochlorothiazide tablets in children below the age of 18 has not been studied in clinical trials. However, olmesartan medoxomil tablets have been shown to be safe and effective in hypertension in children aged 6 to 17 years (see CLINICAL PHARMACOLOGY, Pediatric Patients).

**Pregnancy**

BENICAR HCT Tablets (olmesartan medoxomil-hydrochlorothiazide) should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should be told of the potential risks of use of this medication and to use effective contraception during treatment.

**Lactation**

The milk of lactating rats contains olmesartan. Because of the potential for adverse effects on the nursing 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.

**Pregnancy**

Benicar HCT® Tablets (olmesartan medoxomil-hydrochlorothiazide) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should be told of the potential risks of use of this medication and to use effective contraception during treatment.

**Lactation**

BENICAR HCT Tablets (olmesartan medoxomil-hydrochlorothiazide) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BENICAR HCT Tablets (olmesartan medoxomil-hydrochlorothiazide) is administered to a nursing mother.

**Drug Interactions**

**Drugs that May Affect the Renin-Angiotensin System**

The concomitant administration of drugs with the ability to alter the renin-angiotensin-aldosterone system (e.g., ACE inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory agents) can reduce the effectiveness of BENICAR HCT®. The concomitant administration of such drugs is not recommended.

**Other Antihypertensives**

**Dose Titration by Clinical Effect**

BENICAR HCT® tablets (olmesartan medoxomil-hydrochlorothiazide) should be dosed according to clinical response. Monitoring of serum electrolytes especially potassium and serum creatinine should be performed in patients receiving concomitant therapy with other antihypertensive agents.

**Other Antihypertensives**

**Dosing in Patients with Renal Impairment**

BENICAR HCT® tablets (olmesartan medoxomil-hydrochlorothiazide) should be avoided in patients with severe renal impairment (creatinine clearance ≤15 mL/min).

**Other Antihypertensives**

**Dose Titration by Clinical Effect**

BENICAR HCT® tablets (olmesartan medoxomil-hydrochlorothiazide) should be dosed according to clinical response. Monitoring of serum electrolytes especially potassium and serum creatinine should be performed in patients receiving concomitant therapy with other antihypertensive agents.

**Other Antihypertensives**

**Dosing in Patients with Renal Impairment**

BENICAR HCT® tablets (olmesartan medoxomil-hydrochlorothiazide) should be avoided in patients with severe renal impairment (creatinine clearance ≤15 mL/min).
Azor® (amlodipine and olmesartan medoxomil) tablets

**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 (5.1)].

1 INDICATIONS AND USAGE

Azor is indicated for the treatment of hypertension, alone or with other antihypertensive agents. Azor may also be used as initial therapy in patients who are likely to need multiple antihypertensive agents to achieve their blood pressure goals.

Patients with moderate or severe hypertension are at relatively high risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure, and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be based on considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goal may vary based upon the patient's risk.

Data from an 8-week, placebo-controlled, parallel-group factorial study (see Clinical Studies (14.1) in the full prescribing information) provide estimates of the probability of reaching a blood pressure goal with Azor compared to amlodipine or olmesartan medoxomil monotherapy. The figures below provide estimates of the probability of achieving the targeted systolic or diastolic blood pressure goals with Azor 10/40 mg compared with amlodipine or olmesartan medoxomil monotherapy, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling from all available data of that treatment group. The right tail of each curve is less reliable because of small numbers of subjects with high baseline blood pressures.

For example, a patient with a baseline blood pressure of 160/100 mmHg has about a 48% likelihood of achieving a goal of <140 mmHg (systolic) and a 51% likelihood of achieving a goal of <90 mmHg (diastolic) on monotherapy with olmesartan medoxomil 40 mg and about a 46% likelihood of achieving a goal of <140 mmHg (systolic) and a 60% likelihood of achieving a goal of <90 mmHg (diastolic) on monotherapy with amlodipine 10 mg. The likelihood of achieving these same goals increases to 63% (systolic) and 71% (diastolic) on Azor 5/20 mg, and to 68% (systolic) and 85% (diastolic) on Azor 10/40 mg.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal/Neonatal Morbidity and Mortality

Olmesartan medoxomil. 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 several dozen cases reported in the world literature of patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue Azor as soon as possible.

During the second and third trimesters of pregnancy, these drugs have been associated with fetal injury that includes hypotension, neonatal skull hypoplasia, anuric, reversible or irreversible renal failure, and death. Olmesartan medoxomil has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should discontinue the use of Azor as soon as possible.

5.2 Hypotension in Volume- or Salt-Depleted Patients

Olmesartan medoxomil. Symptomatic hypotension may be anticipated after initiation of treatment with olmesartan medoxomil. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics) may be particularly vulnerable. Initiate treatment with Azor under close medical supervision. If hypotension does occur, place the patient in the supine position and give fluids. A more pronounced hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.3 Vasodilation

Amlodipine. Since the vasodilation attributable to amlodipine in Azor is gradual in onset, acute hypotension or syncope has rarely been a problem except in patients with severe aortic stenosis.

5.4 Patients with Severe Obstructive Coronary Artery Disease

Patients, particularly those with severe obstructive coronary artery disease, may develop increased frequency or duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

5.5 Patients with Congestive Heart Failure

Amlodipine. Calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, diuretics, and digoxin. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsening heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class III/IV heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsening of heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.
5.6 Patients with Impaired Renal Function

Amlodipine. There are no studies in Azor 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 Azor 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 Azor.

5.7 Patients with Hepatic Impairment

Amlodipine. Since amlodipine is metabolized by the liver and the plasma elimination half-life (t1/2) is 56 hours in patients with severely impaired hepatic function, extreme caution when administering Aza to patients with severe hepatic impairment is recommended.

Patients with hepatic impairment have decreased clearance of amlodipine. Starting amlodipine or adding Aza to either component may increase the risk of adverse effects. Administration of Azor at recommended starting doses should be considered in patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.4% (i.e., 79/2078) of patients treated with olmesartan medoxomil and 2.7% (i.e., 202/179) 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% vs). Patients with severe hepatic impairment have decreased clearance of Olmesartan medoxomil. Starting Olmesartan medoxomil or adding it to either component may increase the risk of adverse effects.

5.8 Laboratory Tests

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

5.9 Pregnancy

5.9.1 Pregnancy Category D

Amlodipine. There is no information regarding use in pregnant women. Amlodipine is teratogenic in rats at doses of 150 and 300 times (based on body weight) the maximum recommended human dose.

Olmesartan medoxomil. Oral olmesartan medoxomil at doses of 150 and 300 times (based on body weight) the maximum recommended human dose caused fetal developmental toxicity in rats with increased infant mortality. Oral olmesartan medoxomil at doses of 1000 times (based on body weight) the maximum recommended human dose caused reduced fetal weight and delayed ossification in rats and rabbits. Oral olmesartan medoxomil reduced fetal weight in rabbits at a maternal dose of 100 times (based on body weight) the maximum recommended human dose.

5.10 Nursing Mothers

Both amlodipine and olmesartan medoxomil are excreted in human milk. Because both drugs are known to produce clinically important hypotensive effects in nursing infants, both drugs should be avoided in nursing females.

5.11 Pediatric Use

5.11.1 Children

Both amlodipine and olmesartan medoxomil are excreted in human milk. Because both drugs are known to produce clinically important hypotensive effects in nursing infants, both drugs should be avoided in nursing females.

5.12 Animal Data

5.12.1 Mice, Rats, and Dogs

Amlodipine. There was no evidence of impaired fertility in male or female mice and rats at oral doses of up to 20 and 4 times, respectively, the maximum recommended human dose (MRHD) on a body surface area (BSA) basis. In rats, amlodipine caused a decrease in litter size at the highest dose tested (5 mg/kg/day). In one 2-year carcinogenicity study in rats, amlodipine (up to 10 mg/kg/day) and olmesartan medoxomil (up to 200 mg/kg/day) were well tolerated, with an incidence of adverse events similar to that seen with placebo. In a 1-year carcinogenicity study in mice, 150 mg/kg/day was the highest dose tested. No treatment-related changes in the incidence, severity, or nature of tumors were observed in mice or rats at these dose levels.

5.13 Carcinogenesis, Mutagenesis, Impairment of Fertility

Amlodipine. Long-term carcinogenicity studies of amlodipine were conducted in rats at a dose level of 10 mg/kg/day and in mice at a dose level of 4 mg/kg/day. Amlodipine is a metabolite of the active amlodipine moiety. In a 2-year carcinogenicity study in mice, amlodipine caused increased incidences of thymic lymphoma and submaxillary gland adenoma in both sexes. In a 2-year carcinogenicity study in rats, amlodipine induced a dose-related increase in malignant and benign tumors of the salivary gland in both sexes. Amlodipine also induced a dose-related increase in benign and malignant tumors of the pituitary gland in male rats. In a 1-year carcinogenicity study in rats, administration of amlodipine at 5 mg/kg/day for 52 weeks resulted in an increased incidence of glomerulonephritis in females. Amlodipine administered at 5 mg/kg/day for 1 year caused a decrease in body weight gain, food intake, and mean corpuscular volume and a 20% decrease in the number of sperm in rats. In a 1-year carcinogenicity study in dogs, dogs were administered amlodipine at 5 mg/kg/day for 52 weeks. At this dose, amlodipine induced dose-related increases in benign and malignant tumors of the salivary gland in males and females. Amlodipine also induced a dose-related increase in benign and malignant tumors of the liver in females. Amlodipine administered for 1 year at 5 mg/kg/day caused a decrease in body weight gain and decreased bone formation in both sexes. Amlodipine administered for 1 year at 10 mg/kg/day caused a decrease in body weight gain and decreased bone formation in both sexes.

Olmesartan medoxomil. No studies of olmesartan medoxomil have been conducted in animals. There were no adequate and well-controlled studies in pregnant women. Because olmesartan medoxomil is embryotoxic at doses of 150 and 300 times (based on body weight) the maximum recommended human dose, olmesartan medoxomil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

6 ADVERSE REACTIONS

Adverse Reactions in 24-Week Open-Label Combination Therapy in Hypertensive Patients

6.1 Adverse Reactions in Clinical Trials

Body as a Whole: asthenia, angioedema
Gastrointestinal: vomiting
Musculoskeletal: rhabdomyolysis
Urogenital System: acute renal failure
Skin and Appendages: alopecia, pruritus, urticaria

7 DRUG INTERACTIONS

7.1 Drug Interactions with Aza

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

No drug interaction studies have been conducted with Azor and other drugs, although studies have been conducted with the individual amlodipine and olmesartan medoxomil components of Azor, 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 amiodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amiodipine, but co-administration of amlodipine and maalox® (antacid): Co-administration of the antacid maalox® with a single dose of amiodipine had no significant effect on the pharmacokinetics of amiodipine. Droxidopa: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amiodipine. When amiodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Effect of Amlodipine on Other Agents

Atorvastatin: Co-administration of multiple 10 mg doses of amiodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin. Diclofenac: Co-administration of amlodipine with diclofenac did not change serum diazepam levels or renal clearance in normal volunteers. Ethanol (alcohol): Single and multiple 10 mg doses of amiodipine had no significant effect on the pharmacokinetics of ethanol. Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time. In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitrates, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

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 acetaminophen (Acetaminophen) or aspirin. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 2C9, 2C19, 2C8, 2D6, 2E3, 2C18, 1A2, and 3A4 enzymes; thus, interactions with drugs that inhibit, induce, or are metabolized by those enzymes are not expected.
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 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 mating and 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 Olmesartan 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.

8.3 Nursing Mothers

It is not known whether the amlodipine or olmesartan medoxomil components of Azor are excreted in human milk, but amlodipine is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing 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.

8.4 Pediatric Use

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

Amlodipine. The safety and effectiveness of amlodipine in patients with hepatic impairment have not been established.

8.5 Geriatric Use

Of the total number of subjects in the double-blind clinical study of Azer, 20% (384/1940) were 65 years of age or older and 3% (60/1940) 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. 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.

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 triped 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 20-60 mL/min).

8.8 Black Patients

Of the total number of subjects in the double-blind clinical study of Azer, 25% (481/1940) were black patients. Azer 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.

Overdosage 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, haemodialysis 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 dialysability 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)]

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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 stenoses, 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 (t1/2) 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.
See the family that pulls down BP at Booth #1000

AZOR tablets
antipodine and olmesartan medoxomil
Power plus power

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.

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.
See the family that pulls down BP at
Booth #1000

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.