ON THE BEAT

Obituary

Dr. Edwin G. Krebs, a Nobel laureate whose codiscovery of reversible phosphorylation would ultimately affect research in the fields of heart disease, diabetes, cancer, and nerve disease, died Dec. 21 in Seattle. He was 91.

Dr. Krebs, who spent most of his career at Seattle's University of Washington School of Medicine (he joined the faculty in 1948, 2 years after the school opened), died of complications from progressive heart failure.

Although the Lansing, Iowa, native had designs on becoming a physician when he started his undergraduate studies at the University of Illinois, it was his fascination with research work that motivated him to change course after his graduation from Washington University School of Medicine in St. Louis in 1943.

After serving in the United States Navy during World War II as a medical officer, Dr. Krebs was recruited by the husband-and-wife team of Carl and Gerty Cori (1947 Nobel laureates for their research in carbohydrate metabolism and enzymes) to conduct postdoctoral research in biological chemistry at Washington University.

Dr. Krebs then went to Seattle to take a faculty position in the medical school at the University of Washington.

DR. EDWIN G. KREBS

It was there that he met Dr. Edmond H. Fischer, starting a professional partnership and personal friendship that would last for 60 years.

The two made what Dr. Krebs would later describe as an accidental discovery in the early 1950s: that the enzyme glycogen phosphorylase, which affects the energy in muscle cells, was activated by a chemical reaction with phosphate, and deactivated by its removal. The process became known as reversible phosphorylation.

Subsequent research by Dr. Krebs and

NIH, FDA Join to Speed Therapy Development

Top scientists at the National Institutes of Health and the Food and Drug Administration will be working together more closely in an effort to improve regulatory science and bring new treatments to market sooner.

With more new treatments based on emerging technologies, NIH and FDA scientists must communicate earlier and more often, explained Kathleen Sebelius, secretary of the Department of Health and Human Services. From the beginning of a therapy's development, basic scientists at the NIH should share information with the FDA so that FDA regulators can develop appropriate safety and effectiveness standards early on.

At the same time, FDA scientists can help researchers identify possible safety or quality issues earlier in the process, she said during a news conference to announce the partnership.

"By communicating throughout the process, it will help researchers navigate the regulatory process and give regulators the scientific tools they need to quickly assess a treatment's risks and benefits," Ms. Sebelius said. "For Americans, this is going to mean that new treatments are available sooner."

The initiative calls for the creation of a joint FDA–NIH Leadership Council that will include FDA Commissioner Dr. Margaret A. Hamburg and NIH Director Dr. Francis S. Collins, as well as six senior scientists from each of the two agencies. The NIH and the FDA have also pooled their resources to offer $6.75 million in grants over the next 3 years for research on regulatory science. For example, the agencies are looking for ideas on how the FDA would evaluate safety and effectiveness in new stem cell therapies.

Government officials will be seeking public comment on how the two agencies can improve their collaboration. The NIH and the FDA will hold a public meeting jointly this spring to gather input from industry, patient advocates, and the public.

To bring safe, effective therapies into the market sooner, the science used to develop new therapeutic compounds must be closely connected to the science the FDA uses to review those compounds, said Dr. Collins of the NIH.

—Mary Ellen Schneider

MICARDIS® (telmisartan) tablets 20•40•80 mg

WARNING: AVOID USE IN PREGNANCY
When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, MICARDIS tablets should be discontinued as soon as possible. *See Warnings and Precautions*.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Hypertension

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

Cardiovascular Risk Reduction

MICARDIS is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors.

High risk for cardiovascular events can be evidenced by a history of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or high-risk diabetes (insulin-dependent or non-insulin dependent) with evidence of end-organ damage. MICARDIS can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy).

Studies of telmisartan in this setting do not exclude that it may not preserve a meaningful fraction of the effect of the ACE inhibitor to which it was compared. Consider using the ACE inhibitor first, and, if it is stopped for cough only, consider re-trying the ACE inhibitor after the cough resolves.

Use of telmisartan with an ACE inhibitor is not recommended.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, discontinue MICARDIS tablets as soon as possible [*see Boxed Warning*].

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios 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. Inform mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester that most reports of fetal toxicity have been associated with second and third trimester exposure. Nonetheless, when patients become pregnant or are considering pregnancy, have the patient discontinue the use of MICARDIS tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, MICARDIS should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until 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. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Hypotension

In 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), symptomatic hypotension may occur after initiation of therapy with MICARDIS. Either correct this condition prior to administration of MICARDIS, or start treatment under close medical supervision with a reduced dose.

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.

Hyperkalemia

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Impaired Hepatic Function

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with MICARDIS.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of MICARDIS in patients with unilateral or bilateral renal artery stenosis but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.

The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of MICARDIS and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of MICARDIS and ramipril is not recommended.

ADVERSE REACTIONS

The following adverse reaction is described elsewhere in labeling:

Renal dysfunction upon use with ramipril.

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions 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.

Hypertension

MICARDIS has been evaluated for safety in more than 3700 patients, including 1900 treated for over six months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of MICARDIS (20-160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo.

Adverse events occurring at an incidence of ≥1% in patients treated with MICARDIS and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

Table 1 Adverse Events Occurring at an Incidence of ≥ 1% in Patients Treated with MICARDIS and at a Greater Rate Than in Patients Treated with Placebo

	Telmisartan (n=1455) %	Placebo (n=380) %
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0