ANNOUNCEMENTS

Fifth Basic Sciences Symposium of the Transplantation Society

The Fifth Basic Sciences Symposium of the Transplantation Society will be held at the Chautauqua Institution, Chautauqua, NY, on September 6–11, 1997. Distinguished plenary speakers will update the most relevant topics of transplantation biology, which will be enhanced by oral and poster presentations by interested participants on the following subjects: T-Cell Stimulation and Co-stimulation, T-Cell Signalling Mechanisms, Immune Privilege, Tolerance, Chimerism and Bone Marrow Transplantation, Immunosuppression, Alloreactivity and Rejection, and Newer Experimental Models. The deadline for submission of abstracts was January 31, 1997. For futher information, contact R. Cunningham, Ph.D., The Ernest Witebsky Center for Immunology, School of Medicine and Biomedical Sciences, 233 Sherman Hall, 3435 Main Street, Buffalo, NY 14214-3078. Telephone: 716/829-2901; fax: 716/829-2158; e-mail: rcunning@ubmedb.buffalo.edu.

Second Congress of BANTAO (Balkan Cities Association of Nephrology, Dialysis, Transplantation and Artificial Organs)

The Second Congress of BANTAO will be held September 6–8, 1997, in Struga, Republic of Macedonia. The Congress is sponsored by the European Society for Artificial Organs (ESAO), the International Faculty for Artificial Organs (INFA). The primary topics of the Congress will be epidemiology of renal diseases; acute renal failure (etiopathogenesis and treatment); renal replacement therapy; systemic disease and renal involvement; progress in nephrology (invited symposia); and drugs and the kidney. For further information, contact Prof. M. Polenakovic, Department of Nephrology, Clinical Centre, Medical Faculty, Vodnjanska 17, 91000 Skopje, R. Macedonia. Telephone: ++389 91 112 179; fax: ++389 91 614 486; e-mail: maknefpo@lotus.mpt.com.mk.

Second Congress of the Macedonia Society of Nephrology, Dialysis, Transplantation and Artificial Organs

The Second Congress of the Macedonian Society of Nephrology, Dialysis, Transplantation and Artificial Organs will be held September 8–10, 1997, in Struga, Republic of Macedonia. The Congress is sponsored by the European Society for Artificial Organs (ESAO), the International Society for Artificial Organs (INFA). The primary topics of the Congress will be: epidemiology of renal diseases in the Republic of Macedonia; acute renal failure (etiopathogenesis and treatment); dialysis; pregnancy and the kidney; urinary tract infections; primary and secondary glomerulonephropathies; hypertension; ultrasounds in nephrology; and renal transplantation. For further information, contact Prof. M. Polenakovic, Department of Nephrology, Clinical Centre, Medical Faculty, Vodnjanska 17, 91000 Skopje, R. Macedonia. Telephone: ++389 91 112 179; fax: ++389 91 614 486; e-mail: maknefpo@lotus.mpt.com.mk.

NIDDK Polycystic Kidney Disease (PKD) Workshop

The National Institute of Diabetes and Digestive and Kidney Diseases will hold a Polycystic Kidney Disease (PKD) Workshop at the National Institutes of Health in Bethesda, Maryland, September 10–11, 1997. For information, contact Ms. Andrea Gasper, CCC. Telephone: (301) 493-9674; fax: (301) 493-9674; e-mail: andreag@ccc76.com.

15th Annual Meeting of the International Society of Blood Purification (ISBP)

The 15th Annual Meeting of the International Society of Blood Purification (ISBP) will be held September 11–13, 1997, in Florence, Italy. Topics will include symposia on the myocardium in chronic renal failure, the present status of peritoneal dialysis, and novelties from erythropoietin developments. Free oral/poster communication presentations will be offered on clinical, technical, immunological and metabolic aspects pertaining to all types of blood purification methods. For further information, please contact Prof. Q. Maggiore, Nephrology Unit, S.M. Annunziata Hospital, 50011, Florence, Italy. Fax: +39 55 6449223; e-mail: q.maggiore@trident.nettuno.it.

Renal Biopsy in Medical Diseases of the Kidney

Renal Biopsy in Medical Diseases of the Kidney will be held September 24–27, 1997, at the Columbia-Presbyterian Medical Center, New York, NY. The accredited sponsor for the course is the College of Physicians & Surgeons of Columbia University. Program directors Gerald B. Appel, M.D., Vivette D. D'Agati, M.D., Conrad L. Pirani, M.D., and Fred G. Silva, M.D. will be joined by guest lecturers Charles E. Alpers, M.D., Robert B. Colvin, M.D., William G. Couser, M.D., Agnes Fogo, M.D., Eli Friedman, M.D., Gloria Gallo M.D., Gary S. Hill, M.D., J. Charles Jennette, M.D., Marc A. Pohl, M.D., Helmut G. Rennke, M.D., Burton D. Rose, M.D., Fred G. Silva, M.D., and C. Craig Tisher, M.D. The intensive course is designed for pathologists, nephrologists, internists, and other physicians interested in both a systematic review and an update on advances in diagnostic problems in medical renal diseases. The course should be of special interest to physicians who are preparing for their specialty Board Examinations in Pathology and Clinical Nephrology. Clinicopathological correlations will be emphasized. The format includes lectures, question-and-answer sessions, and the study of case problems. An optional 4-hour renal pathology laboratory exercise is available on Saturday afternoon after the conclusion of the formal lectures. Tuition fees are $595 for physicians, and $395 for fellows and residents in training. These fees include the academic presentations and laboratory session, course syllabus, Kodachrome slides, electronmicrographs of "classic" renal lesions, daily continental breakfast, luncheon, and refreshments. The course qualifies for CME credits of 27.5 credit hours in Category 1, A.M.A.'S Physician's Recognition Award. For further information, contact the Center for Continuing Education, College

of Physicians & Surgeons of Columbia University, 630 West 168th Street, Unit 39, New York, NY 10032. Telephone: 212-781-5990; fax: 212-781-6047.

24th Congress of the European Society For Artificial Organs

The 24th Congress of the European Society For Artificial Organs will be held October 16–18, 1997, in Budapest, Hungary. Main topics will include the pathophysiology of clinical applications of artificial organs, improvement in material properties as a prerequisite for the development of artificial organs, and the importance of auxiliary treatment in artificial organ therapy. For further scientific information, please contact Judit Walter, MD, PhD, President of ESAO 97, Selyemerdö u. l., 6300 Kalocsa, Hungary. Telephone: +36/78/462-782; fax +36/78/465-077. For general information by computer, e-mail: Novis@elender.hu; http://www.elender.hu/~novis/esao.

1st International Congress on Immunointervention in Nephrology

The 1st International Congress on Immunointervention in Nephrology, organized by the Department of Nephrology, Ospedale S. Michele, Cagliari, Italy (P. Altieri, M.D.), and the Division of Nephrology, Ospedale Maggiore IRCCS, Milan, Italy (C. Ponticelli, M.D.), will be held April 30–May 2, 1998, in Cagliari, Sardinia, Italy. The meeting will deal with new therapeutic strategies in kidney transplantation and with clinical and therapeutic aspects of lupus nephritis. Tuition is 250 US$. The deadline for abstract presentation is January 15, 1998. For information contact: Paolo Altieri, M.D., Dipartimento di Nefrologia e Dialisi, Ospedale S. Michele, Via Peretti, 09134 Cagliari (Italy). Telephone and fax: ++39-70-542872 or ++39-70-539491.

XVII World Congress of The Transplantation Society

The XVII World Congress of The Transplantation Society will be held July 12–17, 1998, in Montréal, Canada. The deadline for abstract submission is January 19, 1998. For further information, please contact Lucy Felicissimo & Associates, Inc., 12,449 rue Cousineau, Montréal, Quebec, Canada H4K 1P9. Fax: 514-334-5200.

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(diltiazem HCl) 120-, 180-, 240-, 300-mg Capsules

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No other diltiazem is therapeutically equivalent

Brief Summary of
Prescribing Information as of December 1995A

CARDIZEM® CD
(diltiazem HCl)
Capsules

CONTRAINDICATIONS
CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS
1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3290 patients or 0.40%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem. (See ADVERSE REACTIONS section.)
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS
General
CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.
Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions
Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with other agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)
As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.
Beta-blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.
Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)
Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.
Digitalis. Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)
Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.
Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted, or discontinued.
The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy
Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.
There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.
The following table presents the most common adverse reactions reported in placebo-controlled angina and hypertension trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

CARDIZEM CD Capsule Placebo-Controlled Angina and Hypertension Trials Combined

Adverse Reactions	Cardizem CD (n=607)	Placebo (n=301)
Headache	5.4%	5.0%
Dizziness	3.0%	3.0%
Bradycardia	3.3%	1.3%
AV Block First Degree	3.3%	0.0%
Edema	2.6%	1.3%
ECG Abnormality	1.6%	2.3%
Asthenia	1.8%	1.7%

In clinical trials of CARDIZEM CD capsules, CARDIZEM tablets, and CARDIZEM SR capsules involving over 3200 patients, the most common events (ie, greater than 1%) were edema (4.6%), headache (4.6%), dizziness (3.5%), asthenia (2.6%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.4%), nausea (1.4%), and rash (1.2%).
In addition, the following events were reported infrequently (less than 1%) in angina or hypertension trials:
Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles
Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dyspeusia, dyspepsia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase
Dermatological: Petechiae, photosensitivity, pruritus, urticaria
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties
The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, some characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

Prescribing Information as of December 1995A

Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

ccdb1295Ac

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References: **1.** Cardizem CD prescribing information. **2.** Felicetta JV, Serfer HM, Cutler NR, et al. *Am Heart J.* 1992;123:1022-1026. **3.** Thadani U, Glasser S, Bittar N, Beach CL, Diltiazem CD Study Group. *Am J Cardiol.* 1994;74:9-17. **4.** Food and Drug Administration. *Approved Drug Products With Therapeutic Equivalence Evaluations* (Orange Book), US Dept of Health and Human Services. 15th ed. Washington, DC;1995.

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A UNIQUE HEMODYNAMIC AND SAFETY PROFILE DIFFERENT FROM DIHYDROPYRIDINES

Effective 24-hour control of hypertension or angina

- Reduces blood pressure with no reflex tachycardia[1]
- Increases exercise tolerance, reduces vasospasm, and decreases heart rate in angina[1]

Well-tolerated control regardless of age or gender†

- A side-effect discontinuation rate comparable to placebo[2,3]
- Most commonly reported side effects are headache (5.4%), bradycardia (3.3%), first-degree AV block (3.3%), dizziness (3.0%), edema (2.6%), ECG abnormality (1.6%), and asthenia (1.8%)[1]

True 24-hour control from a unique patented delivery system

- No other diltiazem is therapeutically equivalent to Cardizem CD[4‡]

*Cardizem CD is a benzothiazepine calcium channel blocker.

† In clinical trials with Cardizem CD.
‡ FDA does not, at this time, consider other diltiazems to be therapeutically equivalent because bioequivalence has not been demonstrated through appropriate studies.

Please see brief summary of prescribing information on adjacent page.

FOR HYPERTENSION OR ANGINA

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