

## ON THE BEAT

## Obituaries

**Dr. Adrian Kantrowitz**, who performed the first human heart transplant in the United States, died last month in Ann Arbor, Mich., from complications of heart failure. He was 90.

Although Dr. Kantrowitz enjoyed the distinction of performing that first operation, most of his 60 years of practice and research were focused on developing devices that assisted heart function, rather than replacing weak and malfunctioning hearts. His historic transplant, on Dec. 6, 1967, followed the world's first, by the South African surgeon Christiaan Barnard, by 3 days, and was the culmination of almost 4 years of transplants in dogs.

From early on in his career, Dr. Kantrowitz had collaborated with the late Dr. Michael DeBakey and others, including his wife Jean, in devising new methods for treating and sustaining gravely ill heart patients. These included the development of the left-ventricular assist device, the intra-aortic balloon pump for reducing strain on



Dr. Kantrowitz (right), with Dr. DeBakey (center) and Dr. Bernard (left) in 1967.

the heart; and an early version of the implantable pacemaker.

Dr. Kantrowitz studied mathematics at New York University before attending the Long Island College of Medicine (now State University of New York, Brooklyn). He graduated in 1943 and served for 3 years as a surgeon in the U.S. army medical corps. After specializing in cardiology, he held various positions at Montefiore Hospital (now Montefiore Medical Center) in New York.

In 1955, he became director of cardiovascular surgery at New York's Maimonides Hospital, where he and his fellow researchers invented an electronically controlled heart-lung machine and a diaphragm booster heart that functioned as a second heart. He left Maimonides in 1970, however, after facing questions about his research, and moved to Sinai Hospital in Detroit, where he was an attending surgeon and chairman of the department of surgery. He continued experimenting with transplants, the balloon pump, and partial mechanical hearts.

In 1983 he and his wife cofounded L.VAD Technology, research and development company in Detroit that specialized in cardiovascular devices. The couple was still working on new devices until the end of his life. Shortly before his death, Dr. Kantrowitz received approval from the Food and Drug Administration to proceed

with a clinical trial for a new balloon-pump variant.

**Dr. Mark Silverman**, a consultative cardiologist, teacher, and medical historian, died of a heart attack at Piedmont Hospital in Atlanta, where he had founded the Fuqua Heart Center. He was 69 years of age.

At the time of his death, he was emeritus professor of medicine (cardiology) at Emory University, also in Atlanta, chief of cardiology at the heart center, and director of its noninvasive (electrocardiology, echo, and stress testing) laboratories.



DR. SILVERMAN

its Dutch inventor, the 1924 Nobel laureate, Dr. Willem Einthoven.

Dr. Silverman published a textbook on clinical skills in primary care, numerous articles, and chapters in books on medical

Dr. Silverman was known for his lively lectures, in which he would sometimes dress in period outfits: When teaching about the electrocardiogram, for example, he would dress and speak as

history, a book that explored the relationship between some heart conditions and abnormalities of the hand.

Dr. Silverman received his medical degree from the University of Chicago, after which he returned to his alma mater, Ohio State University, Columbus, for his medical residency. He worked with Dr. Hurst from 1966 to 1968 and, after serving in the U.S. Air Force at David Grant Medical Center at Travis Air Force Base, California, he returned to Atlanta in 1970 as the Emory-Piedmont Professor of Medicine and established a cardiology program at Piedmont Hospital.

—Renée Matthews

### CRESTOR® (rosuvastatin calcium) Tablets

**BRIEF SUMMARY:** For full Prescribing Information, see package insert.

**INDICATIONS AND USAGE** **Hyperlipidemia and Mixed Dyslipidemia** CRESTOR is indicated as adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, nonHDL-C, and triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate. **Hypertriglyceridemia** CRESTOR is indicated as adjunctive therapy to diet for the treatment of adult patients with hypertriglyceridemia. **Homozygous Familial Hypercholesterolemia** CRESTOR is indicated as adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable to reduce LDL-C, Total-C, and ApoB in adult patients with homozygous familial hypercholesterolemia. **Slowing of the Progression of Atherosclerosis** CRESTOR is indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels. **Limitations of Use** The effect of CRESTOR on cardiovascular morbidity and mortality has not been determined. CRESTOR has not been studied in Fredrickson Type I, III, and V dyslipidemias. **DOSAGE AND ADMINISTRATION** **General Dosing Information** The dose range for CRESTOR is 5 to 40 mg orally once daily. CRESTOR can be administered as a single dose at any time of day, with or without food. When initiating CRESTOR therapy or switching from another HMG-CoA reductase inhibitor therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's response and individualized goal of therapy. The 40 mg dose of CRESTOR should be used only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose (see **Warnings and Precautions**). **Hyperlipidemia, Mixed Dyslipidemia, Hypertriglyceridemia and Slowing of the Progression of Atherosclerosis** The recommended starting dose of CRESTOR is 10 mg once daily. For patients with marked hyperlipidemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20 mg starting dose may be considered. After initiation or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and the dosage adjusted accordingly. **Homozygous Familial Hypercholesterolemia** The recommended starting dose of CRESTOR is 20 mg once daily. Response to therapy should be estimated from pre-apheresis LDL-C levels. **Dosage in Asian Patients** Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients (see **Use in Specific Populations and Clinical Pharmacology** in full Prescribing Information (12.3)). **Use with Cyclosporine or Lopinavir/Ritonavir** In patients taking cyclosporine, the dose of CRESTOR should be limited to 5 mg once daily (see **Warnings and Precautions and Drug Interactions**). In patients taking a combination of lopinavir and ritonavir, the dose of CRESTOR should be limited to 10 mg once daily (see **Warnings and Precautions and Drug Interactions**). **Concomitant Lipid-Lowering Therapy** The risk of skeletal muscle effects may be enhanced when CRESTOR is used in combination with niacin or fenofibrate; a reduction in CRESTOR dosage should be considered in this setting (see **Warnings and Precautions and Drug Interactions**). Combination therapy with gemfibrozil should be avoided because of an increase in CRESTOR exposure with concomitant use; if CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily (see **Warnings and Precautions and Drug Interactions**). **Dosage in Patients With Severe Renal Impairment** For patients with severe renal impairment ( $CL_{CR} < 30$  mL/min/1.73 m<sup>2</sup>) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not exceed 10 mg once daily (see **Use in Specific Populations and Clinical Pharmacology** in full Prescribing Information (12.3)). **CONTRAINDICATIONS** CRESTOR is contraindicated in the following conditions:

- Patients with a known hypersensitivity to any component of this product. Hypersensitivity reactions including rash, pruritus, urticaria and angioedema have been reported with CRESTOR (see **Adverse Reactions**).
- Patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels (see **Warnings and Precautions**).
- Women who are pregnant or may become pregnant. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, CRESTOR may cause fetal harm when administered to pregnant women. Additionally, there is no apparent benefit to therapy during pregnancy, and safety in pregnant women has not been established. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued use during pregnancy (see **Use in Specific Populations and Nonclinical Toxicology** in full Prescribing Information (13.2)).
- Nursing mothers. Because another drug in this class passes into breast milk, and because HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, women who require CRESTOR treatment should be advised not to nurse their infants (see **Use in Specific Populations**).

**WARNINGS AND PRECAUTIONS** **Skeletal Muscle Effects** Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including CRESTOR. These risks can occur at any dose level, but are increased at the highest dose (40 mg). CRESTOR should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥ 65 years, inadequately treated hypothyroidism, renal impairment). The risk of myopathy during treatment with CRESTOR may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, or lopinavir/ritonavir (see **Dosage and Administration and Drug Interactions**). CRESTOR therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected. CRESTOR therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Liver Enzyme Abnormalities and Monitoring** It is recommended that liver enzyme tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Increases in serum transaminases (AST [SGOT] or ALT [SGPT]) have been reported with HMG-CoA reductase inhibitors, including CRESTOR. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to CRESTOR therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials. In a pooled analysis of placebo-controlled trials, increases in serum transaminases to > 3 times the upper limit of normal occurred in 1.1% of patients taking CRESTOR versus 0.5% of patients treated with placebo. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of > 3 times ULN persist, reduction of dose or withdrawal of CRESTOR is recommended. CRESTOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease (see **Clinical Pharmacology** in full Prescribing Information (12.3)). Active liver disease, which may include unexplained persistent transaminase elevations, is a contraindication to the use of CRESTOR (see **Contraindications**). **Concomitant Coumarin Anticoagulants** Caution should be exercised when anticoagulants are given in conjunction with CRESTOR because of the potentiation of coumarin-type anti-coagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs (see **Drug Interactions**). **Proteinuria and Hematuria** In the CRESTOR clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among CRESTOR-treated patients. In the CRESTOR controlled clinical trials database (placebo or active-controlled) of 5,394 patients with a mean treatment duration of 15 weeks, 1.4% of patients discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: • myalgia • abdominal pain • nausea. The most commonly reported adverse reactions (incidence ≥ 2%) in the CRESTOR controlled clinical trials database of 5,394 patients were: • headache • myalgia • abdominal pain • asthenia • nausea. **Clinical Studies Experience** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. Adverse reactions reported in ≥ 2% of patients in placebo-controlled clinical studies and at a rate greater than or equal to placebo are shown in Table 1. These studies had a treatment duration of up to 12 weeks.

**ADVERSE REACTIONS** The following serious adverse reactions are discussed in greater detail in other sections of the label: • Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) (see **Warnings and Precautions**) • Liver enzyme abnormalities (see **Warnings and Precautions**). In the CRESTOR controlled clinical trials database (placebo or active-controlled) of 5,394 patients with a mean treatment duration of 15 weeks, 1.4% of patients discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: • myalgia • abdominal pain • nausea. The most commonly reported adverse reactions (incidence ≥ 2%) in the CRESTOR controlled clinical trials database of 5,394 patients were: • headache • myalgia • abdominal pain • asthenia • nausea. **Clinical Studies Experience** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. Adverse reactions reported in ≥ 2% of patients in placebo-controlled clinical studies and at a rate greater than or equal to placebo are shown in Table 1. These studies had a treatment duration of up to 12 weeks.

Table 1. Adverse Reactions\* Reported by ≥ 2% of Patients Treated with CRESTOR and ≥ Placebo in Placebo-Controlled Trials (% of Patients)

Adverse Reactions	CRESTOR 5 mg N=291	CRESTOR 10 mg N=283	CRESTOR 20 mg N=64	CRESTOR 40 mg N=106	Total CRESTOR 5 mg - 40 mg N=744	Placebo N=382
Headache	5.5	4.9	3.1	8.5	5.5	5.0
Nausea	3.8	3.5	6.3	0	3.4	3.1
Myalgia	3.1	2.1	6.3	1.9	2.8	1.3
Asthenia	2.4	3.2	4.7	0.9	2.7	2.6
Constipation	2.1	2.1	4.7	2.8	2.4	2.4

\* Adverse reactions by COSTART preferred term.

Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis. The following laboratory abnormalities have also been reported: dipstick-positive proteinuria and microscopic hematuria (see **Warnings and Precautions**); elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities. In the METEOR study, involving 981 participants treated with rosuvastatin 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years, 5.6% of CRESTOR-treated subjects versus 2.8% of placebo-treated subjects discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: myalgia, hepatic enzyme increased, headache, and nausea (see **Clinical Studies** in full Prescribing Information (14.5)). Adverse reactions reported in ≥ 2% of patients and at a rate greater than or equal to placebo are shown in Table 2.

Table 2. Adverse Reactions\* Reported by ≥ 2% of Patients Treated with CRESTOR and ≥ Placebo in the METEOR Trial (% of Patients)

Adverse Reactions	CRESTOR 40 mg N=700	Placebo N=281
Myalgia	12.7	12.1
Arthralgia	10.1	7.1
Headache	6.4	5.3
Dizziness	4.0	2.8
Blood CPK	2.6	0.7
Abdominal pain	2.4	1.8
ALT > 3x ULN	2.2	0.7

\* Adverse reactions by MedDRA preferred term.

**Postmarketing Experience** The following adverse reactions have been identified during post-approval use of CRESTOR: arthralgia, hepatitis, jaundice and memory loss. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **DRUG INTERACTIONS** **Cyclosporine** Cyclosporine significantly increased rosuvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily (see **Dosage and Administration, Warnings and Precautions, and Clinical Pharmacology** in full Prescribing Information (12.3)). **Gemfibrozil** Gemfibrozil significantly increased rosuvastatin exposure. Therefore, combination therapy with CRESTOR and gemfibrozil should be avoided. If used, do not exceed CRESTOR 10 mg once daily (see **Dosage and Administration and Clinical Pharmacology** in full Prescribing Information (12.3)). **Lopinavir/Ritonavir** The combination of lopinavir and ritonavir significantly increased rosuvastatin exposure. Therefore, in patients taking a combination of lopinavir and ritonavir, the dose of CRESTOR should be limited to 10 mg once daily. The effect of other protease inhibitors on rosuvastatin has not been examined (see **Dosage and Administration, Warnings and Precautions, and Clinical Pharmacology** in full Prescribing Information (12.3)). **Coumarin Anticoagulants** CRESTOR significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with CRESTOR. In patients taking coumarin anticoagulants and CRESTOR concomitantly, INR should be determined before starting CRESTOR and frequently enough during early therapy to ensure that no significant alteration of INR occurs (see **Warnings and Precautions and Clinical Pharmacology** in full Prescribing Information (12.3)). **Niacin** The risk of skeletal muscle effects may be enhanced when CRESTOR is used in combination with niacin; a reduction in CRESTOR dosage should be considered in this setting (see **Warnings and Precautions**). **Fenofibrate** When CRESTOR was coadministered with fenofibrate no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. The benefit of further alterations in lipid levels by the combined use of CRESTOR with fibrates should be carefully weighed against the potential risks of this combination (see **Warnings and Precautions and Clinical Pharmacology** in full Prescribing Information (12.3)). **USE IN SPECIFIC POPULATIONS** **Pregnancy Teratogenic Effects: Pregnancy Category X.** CRESTOR is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy (see **Contraindications**). There are no adequate and well-controlled studies of CRESTOR in pregnant women. There have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified. Rosuvastatin crosses the placenta in rats and rabbits. In rats, CRESTOR was not teratogenic at systemic exposures equivalent to a human therapeutic dose of 40 mg/day. At 10-12 times the human dose of 40 mg/day, there was decreased pup survival, decreased fetal body weight among female pups, and delayed ossification. In rabbits, pup viability decreased and maternal mortality increased at doses equivalent to the human dose of 40 mg/day (see **Nonclinical Toxicology** in full Prescribing Information (13.2)). CRESTOR may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking CRESTOR, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy. **Nursing Mothers** It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. In rats, breast milk concentrations of rosuvastatin are three times higher than plasma levels; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require CRESTOR treatment should be advised not to nurse their infants. (See **Contraindications**) **Pediatric Use** The safety and effectiveness of CRESTOR in pediatric patients have not been established. Treatment experience with CRESTOR in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 8 years of age. In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of CRESTOR. Both  $C_{max}$  and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses. **Geriatric Use** Of the 10,275 patients in clinical studies with CRESTOR, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and 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. Elderly patients are at higher risk of myopathy and CRESTOR should be prescribed with caution in the elderly (see **Warnings and Precautions and Clinical Pharmacology** in full Prescribing Information (12.3)). **Renal Impairment** Rosuvastatin exposure is not influenced by mild to moderate renal impairment ( $CL_{CR} \geq 30$  mL/min/1.73 m<sup>2</sup>); however, exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. CRESTOR dosing should be adjusted in patients with severe renal impairment ( $CL_{CR} < 30$  mL/min/1.73 m<sup>2</sup>) not requiring hemodialysis (see **Dosage and Administration, Warnings and Precautions, and Clinical Pharmacology** in full Prescribing Information (12.3)). **Hepatic Impairment** CRESTOR is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels. Chronic alcohol liver disease is known to increase rosuvastatin exposure; CRESTOR should be used with caution in these patients (see **Contraindications, Warnings and Precautions, and Clinical Pharmacology** in full Prescribing Information (12.3)). **Asian Patients** Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. CRESTOR dosage should be adjusted in Asian patients (see **Dosage and Administration and Clinical Pharmacology** in full Prescribing Information (12.3)). **OVERDOSAGE** There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

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