Eplerenone:
A Selective Aldosterone Receptor Antagonist (SARA)

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**ABSTRACT**

Aldosterone, the final product of the renin-angiotensin-aldosterone system (RAAS), is a mineralocorticoid hormone that classically acts, via the mineralocorticoid (aldosterone) receptor, on epithelia of the kidneys, colon, and sweat glands to maintain electrolyte homeostasis. Aldosterone has also been shown to act at nonepithelial sites where it can contribute to cardiovascular disease such as hypertension, stroke, malignant nephrosclerosis, cardiac fibrosis, ventricular hypertrophy, and myocardial necrosis. Although angiotensin-converting enzyme (ACE) inhibitors and angiotensin type 1 (AT1) receptor antagonists act to suppress the RAAS, these agents do not adequately control plasma aldosterone levels — a phenomenon termed “aldosterone synthesis escape.” Spironolactone, a nonselective aldosterone receptor antagonist, is an effective agent to suppress the actions of aldosterone; its use is, however, associated with progestational and antiandrogenic side effects due to its promiscuous binding to other steroid receptors. For these reasons, eplerenone — the first agent of a new class of drugs known as the selective aldosterone receptor antagonists (SARAs) — is under development. In rodent models, eplerenone provides marked protection against vascular injury in the kidney and heart. In phase II clinical trials, eplerenone demonstrates 24-h control of blood pressure with once or twice daily dosing, and is safe and well tolerated in patients with heart failure when given with standard of care agents. Pharmacokinetic studies reveal that eplerenone has good bioavailability with low protein binding, good plasma exposure, and is highly metabolized to inactive metabolites and excreted principally in the bile. Eplerenone is well tolerated in acute and chronic safety pharmacology studies. Ongoing phase III trials of eplerenone in the treatment of hypertension and heart failure are underway. These studies will extend our understanding of selective aldosterone receptor antagonism in the treatment of chronic cardiovascular disease.