

RESEARCH MONOGRAPH . COMPOUND PROFILE

Eplerenone

A selective aldosterone antagonist derived from the spironolactone scaffold through introduction of a 9-alpha,11-alpha-epoxy group, developed across four pharmaceutical sponsors over two decades and validated in landmark heart failure and post-myocardial infarction trials as the first mineralocorticoid receptor antagonist with clinically meaningful selectivity over sex steroid hormone receptors.

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ABSTRACT

Eplerenone is a steroidal mineralocorticoid receptor (MR) antagonist and the second agent approved in this pharmacological class, reaching United States Food and Drug Administration registration in 2002 (marketed as Inspra) approximately four decades after the introduction of spironolactone, the first-generation nonselective aldosterone blocker. The compound is distinguished from spironolactone by the presence of a 9- α ,11- α -epoxy bridge and a 17- α -carbomethoxy substituent, structural modifications that confer approximately 20- to 40-fold lower binding affinity at the mineralocorticoid receptor but approximately 500- to 800-fold greater selectivity over the androgen, progesterone, and glucocorticoid receptors. This selectivity profile eliminates the gynecomastia, breast pain, menstrual irregularity, and sexual dysfunction that limit spironolactone tolerability in chronic cardiovascular and renal indications.

The clinical evidence base for eplerenone rests on two landmark randomized controlled trials. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), published in 2003 in the *New England Journal of Medicine*, enrolled 6,632 patients with left ventricular dysfunction (ejection fraction 40 percent or less) 3 to 14 days after acute myocardial infarction and demonstrated that eplerenone 25 to 50 mg daily reduced all-cause mortality by 15 percent (relative risk 0.85; 95 percent confidence interval 0.75 to 0.96) and heart failure hospitalization by 15 percent compared to placebo on top of optimal medical therapy. The Eplerenone in Mild Patients

Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), published in 2011 in the New England Journal of Medicine, enrolled 2,737 patients with chronic systolic heart failure (ejection fraction 35 percent or less) and New York Heart Association class II symptoms and demonstrated that eplerenone reduced the composite of cardiovascular death and heart failure hospitalization by 37 percent (hazard ratio 0.63; 95 percent confidence interval 0.54 to 0.74). These trials established eplerenone as a guideline-recommended therapy in heart failure with reduced ejection fraction and in post-myocardial infarction left ventricular dysfunction across all major international cardiovascular society guidelines.

Eplerenone is approved in the United States for hypertension and for heart failure following myocardial infarction with left ventricular dysfunction. The compound is also approved in the European Union, Japan, and multiple additional jurisdictions for heart failure with reduced ejection fraction. The pharmacokinetic profile is characterized by rapid oral absorption (time to maximum plasma concentration approximately 1.5 hours), absolute bioavailability of approximately 69 percent, elimination half-life of 4 to 6 hours, and predominant hepatic metabolism by cytochrome P450 3A4 (CYP3A4) with contributions from CYP3A5. The principal adverse event is dose-dependent hyperkalemia, occurring in approximately 5 to 10 percent of treated patients depending on baseline renal function and concurrent renin-angiotensin-aldosterone system blockade; the risk is substantially increased in patients with estimated glomerular filtration rate below 30 mL/min/1.73 m² and in those with serum potassium above 5.0 mEq/L at baseline. The absence of clinically meaningful gynecomastia (0.7 percent versus 9 to 10 percent for

spironolactone in controlled trials) is the principal tolerability advantage.

This monograph reviews the chemistry, synthesis, and structural pharmacology of eplerenone; the molecular pharmacology at the mineralocorticoid receptor in detail; the comprehensive human pharmacokinetic record; the preclinical pharmacology in cardiac fibrosis, remodeling, and inflammatory models; the clinical evidence base across heart failure, post-myocardial infarction, hypertension, and emerging renal indications; sourcing and quality verification considerations; reconstitution and handling; stack-interaction implications with emphasis on CYP3A4-mediated drug-drug interactions and potassium homeostasis; adverse-event signal with focus on hyperkalemia risk stratification; and a structured comparative assessment of five mineralocorticoid receptor antagonists (spironolactone, finerenone, esaxerenone, canrenone, ocedurenone) against eplerenone on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Eplerenone.

Marketed names: Inspra (Pfizer; United States, European Union, Japan, and multiple additional jurisdictions). Generic eplerenone became available in the United States following patent expiration in 2008, with multiple generic manufacturers supplying the compound.

Development codes: SC-66110 (Searle), CGP 30083 (Ciba-Geigy). The Searle development code is the canonical identifier in the clinical pharmacology literature spanning the late 1980s through FDA registration. The Ciba-Geigy code appears in the earliest synthetic chemistry publications [1].

Chemical Abstracts Service registry number: 107724-20-9.

International Union of Pure and Applied Chemistry name: Methyl (1R,2S,9R,10R,11S,14R,15S,17R)-2,15-dimethyl-5,5'-dioxospiro[18-oxapentacyclo[8.8.0.0(1,17).0(2,7).0(11,15)]octadec-6-ene-14,2'-oxolane]-9-carboxylate. The compound is a spiro-lactone steroid derivative with an epoxide bridge at the 9,11 position of the steroid nucleus.

1.2 Structural class and chemistry

Eplerenone is a steroidal mineralocorticoid receptor antagonist belonging to the pregnane subclass of the steroid family. It is structurally derived from spironolactone through two critical modifications: (1) introduction of a 9- α ,11- α -epoxy bridge across the C-ring of the steroid nucleus, which sterically constrains the A/B ring junction and reduces binding at androgen and progesterone receptors; and (2) replacement of the 17- α -acetylthio group of spironolactone with a 17- α -carbomethoxy group, which further modulates receptor selectivity and metabolic stability [1, 2].

Molecular formula: C₂₄H₃₀O₆.

Molecular weight: 414.49 g/mol (monoisotopic mass 414.2042).

Physical properties: White to off-white crystalline powder. Sparingly soluble in water (approximately 1 mg/mL at 25 degrees Celsius); freely soluble in organic solvents including dimethyl sulfoxide, methanol, and ethanol. Melting point approximately 241 to 243 degrees Celsius. The compound is not hygroscopic under standard storage conditions.

Stereochemistry: Eplerenone contains eight stereocenters inherent to the steroid nucleus and is supplied as a single stereoisomer with the (1R,2S,9R,10R,11S,14R,15S,17R) configuration. The absolute configuration is established by the steroid biosynthetic pathway and is preserved through total synthesis. Investigators acquiring research-grade eplerenone should confirm stereochemical integrity through optical rotation measurement or chiral chromatographic analysis.

1.3 Synthesis

The synthesis of eplerenone proceeds from the spironolactone scaffold through a multi-step transformation. The original Ciba-Geigy synthesis (de Gasparo et al., 1987) introduced the 9- α ,11- α -epoxy group through epoxidation of the corresponding 9(11)-dehydro intermediate using *m*-chloroperoxybenzoic acid or equivalent peracid reagents [1]. The 17- α -carbomethoxy group is installed through saponification of the spironolactone thioester followed by esterification with methanol under acidic conditions. Industrial scale-up proved challenging; the large-scale production of eplerenone was difficult and costly, contributing to the extended timeline from initial synthesis (1984 at Ciba-Geigy) to FDA approval (2002 under Pfizer ownership) [2]. The compound passed through four pharmaceutical sponsors during development: Ciba-Geigy (initial synthesis), Searle (clinical development), Monsanto (brief ownership following Searle acquisition), Pharmacia (following Monsanto-Pharmacia merger), and Pfizer (following Pfizer-Pharmacia merger in 2003). Modern generic manufacturing has optimized the synthetic route for yield and cost, and the compound is now produced by multiple manufacturers at pharmaceutical-grade purity (greater than 99 percent by HPLC).

2. Abstract

Eplerenone (SC-66110) is a selective, competitive antagonist of the mineralocorticoid receptor (MR) that blocks the pathological effects of aldosterone in the cardiovascular system, kidney, and central nervous system while producing minimal cross-reactivity at androgen, progesterone, and glucocorticoid receptors [1, 2, 3]. This selectivity profile distinguishes eplerenone from spironolactone, the first-generation MR antagonist, and is the structural consequence of the 9- α ,11- α -epoxy modification to the steroid C-ring and the 17- α -carbomethoxy substitution.

The compound was first synthesized at Ciba-Geigy in 1984 and underwent a protracted 18-year development program across four pharmaceutical sponsors before receiving FDA approval in September 2002 for the treatment of hypertension [2]. A supplemental indication for heart failure with left ventricular dysfunction following acute myocardial infarction was approved in October 2003 based on the results of the EPHESUS trial [4]. Two pivotal randomized controlled trials established the cardiovascular evidence base. EPHESUS (6,632 patients, published 2003) demonstrated a 15 percent reduction in all-cause mortality (relative risk 0.85; $p = 0.008$) and a 15 percent reduction in heart failure hospitalization in post-myocardial infarction patients with left ventricular ejection fraction 40 percent or less [4]. EMPHASIS-HF (2,737 patients, published 2011) demonstrated a 37 percent reduction in the composite of cardiovascular death or heart failure hospitalization (hazard ratio 0.63; $p < 0.001$) in patients with chronic systolic heart failure and mild (NYHA class II) symptoms [5].

The pharmacokinetic profile is characterized by rapid absorption (T_{max} approximately 1.5 hours), moderate bioavailability (69 percent), a short elimination half-life (4 to 6 hours) necessitating once- or twice-daily dosing, and predominant CYP3A4-mediated hepatic metabolism with no active metabolites of clinical significance [6, 7]. The short half-life and CYP3A4 dependence create clinically important drug-drug interactions with strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir), which are contraindicated in concurrent use.

The principal adverse event is hyperkalemia, which occurred in approximately 5.5 percent of eplerenone-treated patients versus 3.9 percent of placebo patients in the EPHESUS trial and remains the primary safety concern requiring potassium and renal function monitoring throughout therapy [4, 8]. Critically, the rate of gynecomastia or breast pain in men treated with eplerenone is 0.7 to 1.6 percent in controlled trials, compared to 9 to 10 percent with spironolactone in the RALES trial, representing the principal tolerability advantage and the clinical rationale for the development of the compound [9, 10].

Current guideline recommendations from the American College of Cardiology, American Heart Association, European Society of Cardiology, and Heart Failure Society of America position eplerenone (along with spironolactone) as a Class I recommendation in heart failure with reduced ejection fraction (HFrEF) as part of quadruple therapy alongside angiotensin-converting enzyme inhibitors or angiotensin receptor-neprilysin inhibitors, beta-blockers, and sodium-glucose cotransporter 2 inhibitors. The emergence of non-steroidal mineralocorticoid receptor antagonists (finerenone, esaxerenone) has expanded the competitive landscape, particularly in diabetic kidney disease where finerenone has demonstrated renal and cardiovascular benefits in the FIDELIO-DKD and FIGARO-DKD trials, but eplerenone retains its established position in heart failure management.

3. Discovery and Development History

3.1 Origin

The development of eplerenone is inseparable from the broader history of aldosterone antagonism, which began with the introduction of spironolactone by Searle in 1959. Spironolactone, while effective as an aldosterone blocker in heart failure, hypertension, and primary aldosteronism, carried the liability of significant binding to androgen and progesterone receptors, producing gynecomastia, breast tenderness, menstrual irregularities, and impotence at clinically effective doses. The recognition that these adverse effects limited long-term adherence, particularly in the heart failure population, motivated a multi-decade search for a more selective MR antagonist [2].

The Ciba-Geigy research group (de Gasparo and colleagues) synthesized the 9- α ,11- α -epoxide of mexrenone in 1984, producing the compound that would become eplerenone. The rationale was that the epoxy bridge across the C-ring of the steroid nucleus would restrict the conformational flexibility of the A/B ring junction and thereby reduce accommodation in the ligand-binding domains of androgen and progesterone receptors while preserving adequate complementarity at the mineralocorticoid receptor [1, 2]. Phase I studies comparing eplerenone head-to-head with spironolactone were published in 1989, demonstrating natriuretic activity at 50 mg eplerenone roughly equivalent to 25 mg spironolactone, confirming the expected 20- to 40-fold potency reduction relative to spironolactone at the MR [2].

3.2 Development trajectory and sponsor changes

The development of eplerenone was marked by an unusually complex corporate history. Ciba-Geigy conducted the initial synthesis and early pharmacology but did not advance the compound to large-scale clinical development. The compound was transferred to Searle (a division of G.D. Searle and Company), which conducted the principal clinical pharmacology and registration studies. Searle was acquired by Monsanto in 1985; Monsanto merged with Pharmacia and Upjohn in 2000 to form Pharmacia Corporation; and Pharmacia was acquired by Pfizer in 2003 [2]. The

EPHESUS trial was conducted under Pharmacia sponsorship and published in 2003 under Pfizer authorship. The extended 18-year development timeline (1984 to 2002) reflects both the difficulty of large-scale synthesis and the complex corporate transitions.

3.3 Regulatory approval

Eplerenone received FDA approval on September 27, 2002, under NDA 21-437 for the treatment of hypertension, based on two fixed-dose, placebo-controlled, 8- to 12-week monotherapy studies demonstrating blood pressure reductions of 6 to 13 mmHg systolic and 3 to 7 mmHg diastolic at doses of 50 to 200 mg daily [11]. A supplemental NDA (21-437/S-002) was approved on October 8, 2003, for heart failure post-myocardial infarction based on the EPHESUS trial results [4]. European Medicines Agency approval followed in 2004. Generic eplerenone became available in the United States following the expiration of the method-of-use patents; multiple generic manufacturers now supply the compound.

3.4 Position in the MR antagonist development timeline

The time lag between spironolactone registration (1959) and eplerenone registration (2002), a span of over 40 years, represents one of the longest gaps between first-generation and second-generation agents in any pharmacological class. The gap reflects both the difficulty of achieving sufficient MR selectivity within the steroidal scaffold and the absence of clinical urgency before the RALES trial (1999) demonstrated that aldosterone blockade reduced mortality in severe heart failure [9, 10]. The RALES result catalyzed completion of the EPHESUS program and subsequent approval. The third generation of MR antagonists, the non-steroidal agents (finerenone, esaxerenone, ocedurenone), began entering clinical development in the 2010s and is now reshaping the competitive landscape, particularly in diabetic kidney disease.

4. Mechanism of Action

Eplerenone is a competitive antagonist at the mineralocorticoid receptor (MR, also designated NR3C2), a member of the nuclear receptor superfamily of ligand-activated transcription factors. The MR is the physiological receptor for aldosterone, a steroid hormone produced by the zona glomerulosa of the adrenal cortex under the regulation of the renin-angiotensin-aldosterone system (RAAS) and plasma potassium concentration.

4.1 Mineralocorticoid receptor pharmacology

The MR is expressed in classical epithelial tissues (distal nephron, colon, salivary glands, sweat glands) where it regulates sodium reabsorption and potassium excretion, and in non-epithelial tissues (cardiomyocytes, vascular smooth muscle cells, endothelial cells, macrophages, fibroblasts, hippocampal and hypothalamic neurons, and adipocytes) where it mediates pathological effects under conditions of aldosterone excess, oxidative stress, or tissue injury [3, 12].

In the classical renal epithelial pathway, aldosterone binds the cytoplasmic MR, induces receptor conformational change and dissociation from the heat shock protein chaperone complex, promotes receptor dimerization, nuclear translocation, and binding to hormone response elements in the promoters of target genes including the epithelial sodium channel (ENaC, encoded by SCNN1A, SCNN1B, SCNN1G), the Na⁺/K⁺-ATPase, and serum- and glucocorticoid-regulated kinase 1 (SGK1). The net epithelial effect is sodium retention and potassium excretion [3, 12].

In non-epithelial tissues, particularly in the cardiovascular system, MR activation under conditions of high aldosterone, high salt intake, or oxidative stress promotes a distinct set of pathological responses: myocardial and vascular fibrosis through upregulation of collagen I and III synthesis, proinflammatory cytokine production (interleukin-6, monocyte chemoattractant protein-1, tumor necrosis factor alpha), endothelial dysfunction through reduced nitric oxide bioavailability, vascular smooth muscle cell proliferation and hypertrophy, and platelet activation [3, 12, 13]. These non-epithelial MR-mediated effects constitute the pathological substrate that aldosterone antagonists target in heart failure and cardiovascular disease.

4.2 Eplerenone binding and selectivity

Eplerenone binds the MR ligand-binding domain with an IC₅₀ of approximately 24 nanomolar (radioligand displacement) and a K_i of approximately 0.08 to 0.81 nanomolar in functional transactivation assays, depending on the cellular context and reporter system [3, 14]. Compared to spironolactone, eplerenone has approximately 20- to 40-fold lower affinity at the MR, necessitating higher clinical doses (25 to 50 mg versus 12.5 to 50 mg for spironolactone) for equivalent MR blockade.

The selectivity advantage is quantitative and clinically meaningful. In competitive binding assays, eplerenone shows the following approximate selectivity ratios relative to MR binding: androgen receptor, 500- to 800-fold selectivity; progesterone receptor, 500- to 800-fold selectivity; glucocorticoid receptor, greater than 1000-fold selectivity [3, 14]. By comparison, spironolactone shows only 3- to 7-fold selectivity over the androgen and progesterone receptors, which is insufficient to prevent clinically significant antiandrogenic and progestational effects at therapeutic MR-blocking doses [3].

Molecular modeling and X-ray crystallographic studies of the MR ligand-binding domain have elucidated the structural basis for the selectivity differential. The 9- α ,11- α -epoxy bridge of eplerenone introduces a rigid planar element in the C-ring that creates steric clashes with residues in the androgen receptor and progesterone receptor ligand-binding pockets that are not present in the more accommodating MR pocket. The 17- α -carbomethoxy group further disfavors androgen and progesterone receptor binding through electrostatic and steric effects [14].

4.3 Downstream cardiovascular and renal effects

The therapeutic consequences of MR blockade by eplerenone in the cardiovascular system include: reduction of myocardial fibrosis and cardiac remodeling through suppression of collagen synthesis, matrix metalloproteinase activation, and transforming growth factor beta signaling; reduction of vascular inflammation through suppression of macrophage MR-mediated proinflammatory cytokine production; improvement of endothelial function through restoration of nitric oxide bioavailability; reduction of oxidative stress through suppression of NADPH oxidase activation; and attenuation of sympathetic nervous system activation [3, 12, 13, 15].

In the kidney, MR blockade reduces sodium reabsorption in the distal nephron (producing natriuresis and mild diuresis), reduces potassium excretion (the basis for the hyperkalemia risk), and in emerging evidence reduces glomerular and tubulointerstitial fibrosis through suppression of the same proinflammatory and profibrotic pathways operative in the cardiovascular system [12, 16].

4.4 Genomic and non-genomic mechanisms

The classical mechanism of MR antagonism is genomic: eplerenone prevents aldosterone-induced MR nuclear translocation and transcriptional activation, with effects emerging over hours to days. Emerging evidence indicates that MR also mediates rapid, non-genomic signaling through interactions with membrane-associated signaling complexes, including activation of EGFR transactivation, ERK1/2 phosphorylation, and intracellular calcium signaling [12]. The contribution of non-genomic MR antagonism to the clinical effects of eplerenone is not fully characterized but may be relevant to the acute hemodynamic and anti-inflammatory responses observed in clinical studies.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Eplerenone is well absorbed after oral administration. Absolute bioavailability is approximately 69 percent, and absorption is not significantly affected by food [6, 7]. Peak plasma concentration (C_{max}) is achieved at approximately 1.5 hours (T_{max}) after oral dosing. Both C_{max} and area under the plasma concentration-time curve (AUC) are dose-proportional over the 25 to 100 mg dose range and less than dose-proportional at doses above 100 mg [6, 11].

5.2 Distribution

The volume of distribution at steady state is approximately 43 to 90 liters (approximately 0.6 to 1.3 L/kg), indicating moderate tissue distribution. Plasma protein binding is approximately 50 percent, primarily to alpha-1-acid glycoprotein. Eplerenone does not preferentially bind to red blood cells. Steady-state plasma concentrations are achieved within 2 days of once-daily dosing [6, 7].

5.3 Metabolism

Eplerenone is metabolized predominantly in the liver by cytochrome P450 3A4 (CYP3A4), with contributions from CYP3A5. The principal metabolic transformations are oxidation at the 6-beta and 21 positions, producing 6-beta-hydroxyeplerenone (primarily via CYP3A4) and 21-hydroxyeplerenone (via both CYP3A4 and CYP3A5) [7, 17]. No active metabolites have been identified at clinically significant concentrations. Less than 5 percent of an administered dose is recovered as unchanged drug in urine and feces, confirming the predominance of metabolic elimination [6].

The CYP3A4 dependence creates important drug-drug interaction potential. Strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, nelfinavir) substantially increase eplerenone exposure: ketoconazole 200 mg twice daily increased eplerenone AUC by 441 percent in a pharmacokinetic interaction

study [6, 11]. Concurrent use of eplerenone with strong CYP3A4 inhibitors is contraindicated. Moderate CYP3A4 inhibitors (erythromycin, verapamil, fluconazole, saquinavir) increase eplerenone AUC by approximately 100 to 200 percent and require dose reduction to a maximum of 25 mg daily [6].

CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) decrease eplerenone exposure. Rifampin reduced eplerenone AUC by approximately 24 percent in interaction studies [6].

The relative role of CYP3A5 versus CYP3A4 has been further characterized in in vitro studies. The 21-hydroxy metabolite is formed preferentially via CYP3A5 (V_{max}/K_M ratio 3.3 versus 1.9 for CYP3A4), while 6-beta-hydroxylation is predominantly CYP3A4-mediated [17]. CYP3A5 polymorphism (the CYP3A5*3 allele, present in approximately 80 to 90 percent of European-ancestry populations, confers absent or reduced CYP3A5 expression) may influence individual eplerenone pharmacokinetics, though the clinical significance of this polymorphism has not been established in outcome studies.

5.4 Elimination

The plasma elimination half-life is approximately 4 to 6 hours. Apparent plasma clearance is approximately 10 L/h. Elimination is predominantly metabolic; renal excretion of unchanged drug accounts for less than 5 percent of the administered dose. Approximately 32 percent of the dose is recovered in feces and 67 percent in urine as metabolites [6, 7].

5.5 Routes of administration

Eplerenone is administered exclusively by the oral route. The compound is formulated as film-coated tablets in 25 mg and 50 mg strengths. No intravenous, intramuscular, or subcutaneous formulations are commercially available. Research-grade eplerenone for in vitro and animal studies is typically dissolved in dimethyl sulfoxide (DMSO) for stock preparation and diluted into aqueous vehicles for administration.

5.6 Special populations

Renal impairment: No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance 30 to 80 mL/min), though the risk of hyperkalemia increases with declining renal function. Eplerenone is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min for the hypertension indication and below 30 mL/min for heart failure) [6, 11].

Hepatic impairment: In patients with moderate hepatic impairment (Child-Pugh Class B), the AUC of eplerenone was increased by approximately 3.6 percent, which is not clinically significant. No dose adjustment is recommended for mild to moderate hepatic impairment. The compound has not been studied in severe hepatic impairment (Child-Pugh Class C) [6].

Elderly: No dose adjustment is required based on age. Population pharmacokinetic analyses from the EPHESUS trial did not identify age as a clinically significant covariate [6].

Pediatric: Eplerenone pharmacokinetics in pediatric populations have not been formally characterized. The compound is not approved for pediatric use.

6. Preclinical Pharmacology

6.1 Cardiac fibrosis and remodeling models

The preclinical pharmacology of eplerenone has been extensively characterized in animal models of cardiac fibrosis, ventricular remodeling, and heart failure. In the deoxycorticosterone acetate (DOCA)-salt hypertensive rat model, eplerenone (100 mg/kg/day) prevented the development of cardiac fibrosis, reduced left ventricular collagen content, and attenuated perivascular inflammation to a degree comparable to spironolactone at equi-effective MR-blocking doses [13, 15].

In the Dahl salt-sensitive rat model of hypertensive heart failure, eplerenone administered at 10, 30, and 100 mg/kg/day from the left ventricular hypertrophy stage to the failing stage produced dose-dependent reductions in left ventricular mass index, myocardial collagen fraction, and expression of proinflammatory and profibrotic genes including transforming growth factor beta-1, connective tissue growth factor, and plasminogen activator inhibitor-1 [15, 18].

In the transverse aortic constriction (TAC) mouse model of pressure-overload heart failure, eplerenone (100 mg/kg/day) attenuated left ventricular dilatation, preserved ejection fraction, reduced interstitial fibrosis, and decreased macrophage infiltration compared to vehicle-treated animals [18]. The antifibrotic effect was associated with suppression of the mineralocorticoid receptor/interleukin-1-beta/vascular endothelial growth factor A (MR/IL-1-beta/VEGFA) signaling pathway.

6.2 Post-myocardial infarction models

In rat coronary artery ligation models of myocardial infarction, eplerenone initiated in the acute (24 to 72 hour) or subacute (7 to 14 day) post-infarction period reduced infarct expansion, attenuated left ventricular dilatation, preserved systolic function, and reduced peri-infarct fibrosis. The effect was additive with angiotensin-converting enzyme inhibitor therapy, supporting the clinical combination used in the EPHESUS trial [15, 19].

6.3 Vascular and endothelial models

Eplerenone has demonstrated vascular protective effects in multiple models. In apolipoprotein E-knockout mice on a high-fat diet, eplerenone reduced aortic atherosclerotic plaque area, reduced macrophage infiltration of plaques, and improved endothelium-dependent vasorelaxation [13]. In stroke-prone spontaneously hypertensive rats, eplerenone reduced cerebrovascular remodeling and reduced stroke incidence independently of blood pressure reduction [15].

6.4 Renal fibrosis models

In the unilateral ureteral obstruction (UUO) rat model, eplerenone prevented renal interstitial fibrosis by inhibiting angiogenesis and endothelial-to-mesenchymal transition through suppression of the MR/IL-1-beta/VEGFA signaling pathway [20]. This finding has supported the investigation of eplerenone and other MR antagonists in chronic kidney disease and diabetic nephropathy.

6.5 Anti-inflammatory models

Eplerenone reduces oxidative stress and inflammation in multiple preclinical systems. In isoproterenol-induced myocardial infarction in rats, eplerenone attenuated cardiac dysfunction and oxidative stress through reduction of lipid peroxidation (malondialdehyde), restoration of antioxidant enzyme activity (superoxide dismutase, catalase, glutathione peroxidase), and suppression of NF-kappaB-mediated inflammatory gene expression [21].

7. Clinical Evidence Base

7.1 Heart failure with reduced ejection fraction: EPHESUS

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was a randomized, double-blind, placebo-controlled trial enrolling 6,632 patients at 674 centers in 37 countries [4]. Eligible patients had experienced acute myocardial infarction 3 to 14 days before randomization, had left ventricular ejection fraction of 40 percent or less, and had clinical evidence of heart failure (pulmonary rales, pulmonary venous congestion on chest radiography, or a third heart sound) or diabetes mellitus. Patients were randomized to eplerenone (titrated from 25 mg daily to a target of 50 mg daily) or matching placebo on top of optimal medical therapy (87 percent on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 75 percent on beta-blockers, 60 percent on aspirin, 47 percent on statins).

The primary endpoints were all-cause mortality and the composite of cardiovascular death or first hospitalization for cardiovascular events. During a mean follow-up of 16 months, eplerenone reduced all-cause mortality from 16.7 percent to 14.4 percent (relative risk 0.85; 95 percent confidence interval 0.75 to 0.96; $p = 0.008$). The composite of cardiovascular death or cardiovascular hospitalization was reduced from 30.0 percent to 26.7 percent (relative risk 0.87; 95 percent confidence interval 0.79 to 0.95; $p = 0.002$). Sudden cardiac death, a prespecified secondary endpoint, was reduced by 21 percent (relative risk 0.79; $p = 0.03$) [4].

7.2 Heart failure with reduced ejection fraction: EMPHASIS-HF

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) was a randomized, double-blind, placebo-controlled trial enrolling 2,737 patients with chronic systolic heart failure (ejection fraction 35 percent or less, NYHA class II symptoms) at 278 centers in 29 countries [5]. Patients were randomized to eplerenone (titrated from 25 mg daily to a target of 50 mg daily) or matching placebo on top of guideline-recommended therapy. The trial was stopped early at a prespecified interim analysis after a median follow-up of 21 months.

The primary endpoint, cardiovascular death or first hospitalization for heart failure, occurred in 18.3 percent of eplerenone patients versus 25.9 percent of placebo patients (hazard ratio 0.63; 95 percent confidence interval 0.54 to 0.74; $p < 0.001$). All-cause mortality was reduced from 12.5 percent to 10.8 percent, though this did not reach statistical significance in isolation (hazard ratio 0.76; 95 percent confidence interval 0.61 to 0.94; $p = 0.01$ by nominal criteria but $p = 0.008$ by one-sided sequential monitoring boundary). First hospitalization for heart failure was reduced by 42 percent (hazard ratio 0.58; 95 percent confidence interval 0.47 to 0.70; $p < 0.001$) [5].

Subgroup analyses from EMPHASIS-HF have demonstrated that the benefit of eplerenone was consistent across prespecified subgroups including age, sex, ejection fraction, NYHA class, baseline renal function, and background therapy. A subgroup analysis published in 2015 found that clinical benefit was particularly pronounced when eplerenone was initiated shortly after hospital discharge, supporting early initiation in clinical practice [22].

7.3 Hypertension

Eplerenone was initially approved for hypertension based on two fixed-dose, placebo-controlled, 8- to 12-week monotherapy studies in 751 patients with baseline diastolic blood pressures of 95 to 114 mmHg [11]. Eplerenone 50 to 200 mg daily produced placebo-adjusted reductions in sitting systolic blood pressure of 6 to 13 mmHg and in sitting diastolic blood pressure of 3 to 7 mmHg. The dose-response relationship was relatively flat across the 50 to 400 mg range, suggesting that maximal antihypertensive effect is achieved at moderate doses. Twenty-four-hour ambulatory blood pressure monitoring confirmed sustained blood pressure reduction throughout the dosing interval [11, 23].

The antihypertensive efficacy of eplerenone is comparable in magnitude to that of thiazide diuretics, angiotensin-converting enzyme inhibitors, calcium channel blockers, and beta-blockers. Eplerenone has demonstrated particular utility in resistant hypertension, where aldosterone excess contributes to treatment resistance. Studies of add-on eplerenone in patients with uncontrolled blood pressure on three or more antihypertensive agents have demonstrated additional systolic blood pressure reductions of 8 to 12 mmHg [23, 24].

7.4 Primary aldosteronism

Eplerenone has been studied as a medical alternative to adrenalectomy in patients with primary aldosteronism (Conn syndrome) who are not surgical candidates or who have bilateral adrenal hyperplasia. While spironolactone remains the first-line medical therapy for primary aldosteronism due to its greater MR potency, eplerenone provides a tolerable alternative for patients who develop intolerable gynecomastia or other sex hormone-related adverse effects on spironolactone [25]. Head-to-head studies indicate that spironolactone is more effective than eplerenone at lowering blood pressure in primary aldosteronism, likely reflecting the potency differential at the MR.

7.5 Emerging renal indications

Eplerenone has been investigated in chronic kidney disease and diabetic nephropathy. The EVALUATE trial studied eplerenone 50 mg daily versus placebo in 336 patients with chronic kidney disease and demonstrated a significant reduction in urinary albumin-to-creatinine ratio without a significant increase in serum potassium above 6.0 mEq/L [16]. However, the development of renal indications for steroidal MR antagonists has been substantially overtaken by the non-steroidal MR antagonist finerenone, which has demonstrated superior renal and cardiovascular outcomes in the FIDELIO-DKD and FIGARO-DKD trials in patients with diabetic kidney disease [26, 27].

7.6 Additional cardiovascular indications

Eplerenone has been studied in hypertrophic cardiomyopathy, with a randomized controlled trial assessing the effect of eplerenone on myocardial fibrosis as measured by cardiovascular magnetic resonance. The compound has also been investigated in pulmonary arterial hypertension, where it attenuated pathological pulmonary vascular remodeling in preclinical models, though clinical translation in this indication remains limited [28].

8. Sourcing and Quality Verification

Pharmaceutical-grade eplerenone is widely available as the FDA-approved product Inspra (Pfizer) and as multiple generic formulations in 25 mg and 50 mg film-coated tablets. The pharmaceutical-grade material meets United States Pharmacopeia (USP) standards for identity, potency, dissolution, and impurity profile.

Research-grade eplerenone is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, Selleckchem, MedChemExpress, Santa Cruz Biotechnology, Tocris, and others) at greater than 98 percent purity by HPLC. Supply is typically in milligram to gram quantities as the free compound (not a salt form). Pricing is moderate, in the range of \$30 to \$150 per gram of research-grade material at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography (HPLC) area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (415.21 for [M+H]⁺ or 437.19 for [M+Na]⁺)
- Nuclear magnetic resonance spectroscopy (¹H and ¹³C) confirmation of structure, particularly the characteristic epoxide proton resonances at the 9,11 position
- Melting point determination (241 to 243 degrees Celsius)
- Karl Fischer titration or loss-on-drying analysis for residual water content

Third-party analytical confirmation is advisable for critical in vivo studies. The eplerenone research supply market is well established and counterfeit material is uncommon, but lot-to-lot variability in purity and residual solvent content has been observed, and on-receipt analytical confirmation is appropriate.

9. Reconstitution and Handling

Eplerenone is sparingly soluble in water (approximately 1 mg/mL at 25 degrees Celsius) but is freely soluble in organic solvents. For in vitro research applications, stock solutions are typically prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM (4.15 to 41.5 mg/mL). DMSO stocks should be aliquoted for single use to avoid repeated freeze-thaw cycles and stored at minus 20 degrees Celsius, where they are stable for at least 12 months.

For cell-based assays, DMSO stock is diluted into culture medium at a final DMSO concentration of 0.1 percent or less to minimize vehicle cytotoxicity. Eplerenone is stable in culture medium at 37 degrees Celsius for at least 24 hours at micromolar concentrations.

For in vivo animal studies, eplerenone is typically administered by oral gavage as a suspension in 0.5 percent methylcellulose or as a solution in a polyethylene glycol-based vehicle (PEG 400). The compound can also be incorporated into rodent chow at defined concentrations for chronic dosing studies. Doses in preclinical studies typically range from 10 to 200 mg/kg/day in rodents, corresponding to human-equivalent doses of approximately 1 to 30 mg/kg/day by allometric scaling [15, 18].

Solid eplerenone should be stored at room temperature (15 to 30 degrees Celsius) in a dry environment, protected from light. The pharmaceutical-grade tablets (Inspra) are stable through the labeled expiration date when stored under recommended conditions. Research-grade powder should be used within the timeframe specified by the supplier certificate of analysis, typically 2 to 3 years from manufacture.

10. Stack Interactions and Combinations

Eplerenone interacts with several drug classes through its CYP3A4-mediated metabolism and through its effects on potassium homeostasis and the renin-angiotensin-aldosterone system. Investigators and clinicians should consider the following interaction profiles:

Strong CYP3A4 inhibitors (contraindicated): Ketoconazole, itraconazole, clarithromycin, nefazodone, ritonavir, and nelfinavir substantially increase eplerenone exposure (ketoconazole increased AUC by 441 percent). Concurrent use is contraindicated [6, 11].

Moderate CYP3A4 inhibitors (dose adjustment required): Erythromycin, verapamil, fluconazole, diltiazem, and saquinavir increase eplerenone AUC by approximately 100 to 200 percent. The maximum recommended eplerenone dose with concurrent moderate CYP3A4 inhibitors is 25 mg daily [6].

CYP3A4 inducers (efficacy reduction): Rifampin, carbamazepine, phenytoin, phenobarbital, and St. John's wort reduce eplerenone exposure. Concurrent use may necessitate eplerenone dose increase or selection of an alternative agent [6].

Potassium-sparing diuretics (contraindicated in combination): Amiloride, triamterene, and spironolactone should not be used concurrently with eplerenone due to additive hyperkalemia risk [11].

ACE inhibitors and angiotensin receptor blockers: Concurrent use is standard practice in heart failure management (per EPHESUS and EMPHASIS-HF protocols), but the combination increases hyperkalemia risk. Potassium monitoring every 2 to 4 weeks during the first 3 months and quarterly thereafter is recommended [4, 5, 11].

Nonsteroidal anti-inflammatory drugs (NSAIDs): NSAIDs reduce renal prostaglandin-mediated potassium excretion and can potentiate eplerenone-induced hyperkalemia. Concurrent use should be accompanied by enhanced potassium monitoring [11].

Lithium: Eplerenone may reduce lithium clearance. Lithium levels should be monitored when initiating or adjusting eplerenone in patients on lithium therapy [6].

SGLT2 inhibitors: The combination of eplerenone with sodium-glucose cotransporter 2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) is now standard in heart failure management as part of guideline-directed quadruple therapy. SGLT2 inhibitors may modestly reduce the hyperkalemia risk associated with MR antagonist therapy through their natriuretic and kaliuretic effects, though this interaction has not been prospectively validated in a dedicated pharmacokinetic study [29].

Digoxin: Eplerenone increased the AUC of digoxin by 16 percent in a pharmacokinetic interaction study. While this increase is generally not clinically significant, digoxin levels should be monitored in patients at the upper end of the therapeutic range [6].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events in controlled clinical trials at approved doses (25 to 50 mg daily) are:

- Hyperkalemia (serum potassium greater than 5.5 mEq/L): 5.5 percent versus 3.9 percent placebo in EPHESUS; 11.8 percent versus 7.2 percent placebo in EMPHASIS-HF [4, 5]
- Dizziness: 3 percent
- Diarrhea: 2 percent
- Cough: 2 percent
- Fatigue: 2 percent
- Influenza-like symptoms: 2 percent

11.2 Hyperkalemia: risk stratification and management

Hyperkalemia is the primary safety concern with eplerenone therapy and the principal dose-limiting adverse event. Risk factors for clinically significant hyperkalemia (serum potassium greater than or equal to 6.0 mEq/L) include: baseline estimated glomerular filtration rate below 30 mL/min/1.73 m²; baseline serum potassium above 5.0 mEq/L; concurrent ACE inhibitor or ARB therapy (standard in heart failure); concurrent potassium supplementation; diabetes mellitus (particularly with diabetic nephropathy); and concurrent NSAID use [4, 5, 8, 11].

In the EPHESUS trial, serious hyperkalemia (potassium greater than or equal to 6.0 mEq/L) occurred in 5.5 percent of eplerenone patients versus 3.9 percent of placebo patients. However, serious hypokalemia (potassium less than 3.5 mEq/L) was significantly more common in the placebo group (14.7 percent versus 8.4 percent), reflecting the potassium-sparing benefit of eplerenone in patients receiving diuretics [4].

Management of hyperkalemia during eplerenone therapy includes dose reduction (from 50 mg to 25 mg daily), temporary discontinuation, dietary potassium restriction, and optimization of loop diuretic therapy. Potassium monitoring is recommended at baseline, at 1 week, at 1 month, and quarterly thereafter, with more frequent monitoring during dose titration or changes in renal function [11].

11.3 Gynecomastia and sex hormone-related adverse events

The selectivity of eplerenone over androgen and progesterone receptors translates directly into a favorable sex hormone-related adverse-event profile compared to spironolactone. In controlled clinical trials of eplerenone lasting 6 months or longer, the rates of gynecomastia, mastodynia, or either in men were 0.7 percent, 1.3 percent, and 1.6 percent, respectively [6, 10]. By comparison, the rate of gynecomastia in men in the RALES trial of spironolactone was 10 percent, and the rate in men with essential hypertension treated with spironolactone has been reported at 6.9 percent [9, 10]. Eplerenone has been used as a substitute in patients who developed gynecomastia on spironolactone, with resolution of breast symptoms in the majority of cases [30].

11.4 Renal function

Eplerenone can produce modest increases in serum creatinine, reflecting reduced renal perfusion in the context of natriuresis and reduced afterload. In the EPHESUS trial, the mean increase in serum creatinine was 0.06 mg/dL greater in the eplerenone group than in the placebo group. Clinically significant acute kidney injury is uncommon but should be monitored, particularly in patients with preexisting renal impairment or concurrent RAAS blockade [4, 8].

11.5 Hepatic effects

No clinically significant hepatotoxicity has been reported with eplerenone. Transaminase elevations have not been observed at rates exceeding placebo in controlled trials [6].

11.6 Pregnancy and lactation

Eplerenone is classified as FDA pregnancy category B (animal reproduction studies have not demonstrated a fetal risk, but there are no adequate and well-controlled studies in pregnant women). In animal reproductive toxicity studies, eplerenone at doses up to 32 times the human therapeutic dose did not produce teratogenicity or embryotoxicity in rats or rabbits [6]. Data on eplerenone excretion in human milk are not available; the compound is present in rat milk. Use during lactation should be approached with caution.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five mineralocorticoid receptor antagonists against eplerenone, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal MR antagonists with substantive clinical or late-stage preclinical evidence, spanning both steroidal and non-steroidal structural classes.

12.1 Spironolactone

Mechanism: Non-selective steroidal mineralocorticoid receptor antagonist with significant binding at androgen receptors (antiandrogenic), progesterone receptors (progestational), and, to a lesser extent, glucocorticoid receptors. Spironolactone is a prodrug, converted to the active metabolite canrenone and to 7- α -thiomethylspironolactone in the liver [9, 10].

Clinical evidence: The Randomized Aldactone Evaluation Study (RALES), published in 1999, randomized 1,663 patients with severe heart failure (NYHA class III or IV, ejection fraction 35 percent or less) to spironolactone 25 mg daily or placebo. Spironolactone reduced all-cause mortality by 30 percent (relative risk 0.70; $p < 0.001$), establishing aldosterone blockade as a mortality-reducing strategy in heart failure and catalyzing the development of eplerenone through the EPHESUS program [9].

Novelty: Low. Spironolactone is the original MR antagonist, introduced in 1959. Its pharmacology is well characterized and its limitations are well understood.

Effect size: Large in severe heart failure (RALES: 30 percent mortality reduction). Direct comparison to eplerenone effect sizes (EPHESUS: 15 percent mortality reduction, EMPHASIS-HF: 37 percent composite reduction) is confounded by different patient populations (NYHA III/IV versus post-MI and NYHA II).

Promising potential: Moderate. Spironolactone remains the most widely prescribed MR antagonist globally, is available as a low-cost generic, and retains guideline-recommended status in heart failure. However, it faces competitive pressure from eplerenone for tolerability and from finerenone for renal indications.

Side-effect profile: The principal limitation is sex hormone-related adverse events. Gynecomastia occurred in 10 percent of men in RALES, breast pain in 21 percent in comparative studies, and menstrual irregularities in premenopausal women [9, 10]. Hyperkalemia rates are comparable to eplerenone at equivalent MR-blocking doses.

Overall validation: High. RALES is a landmark trial and spironolactone has the longest clinical track record of any MR antagonist. The compound is inexpensive and universally available.

Comparison to eplerenone: Spironolactone has greater MR potency, a longer track record, and a stronger mortality signal in severe heart failure (RALES). Eplerenone has superior selectivity, substantially lower rates of gynecomastia and sex hormone-related adverse events, and evidence in the post-MI (EPHESUS) and mild heart failure (EMPHASIS-HF) populations that spironolactone lacks from dedicated randomized trials. The choice between the two in clinical practice is driven primarily by tolerability: spironolactone is first-line in most guidelines due to cost and evidence, with eplerenone reserved for patients who develop intolerable gynecomastia or sex hormone-related adverse effects.

12.2 Finerenone (BAY 94-8862, Kerendia)

Mechanism: Non-steroidal mineralocorticoid receptor antagonist. Finerenone binds the MR with potency comparable to spironolactone but is structurally unrelated to steroids, eliminating sex hormone receptor cross-reactivity by an entirely different structural strategy than the eplerenone approach. Finerenone has a shorter half-life (2 to 3 hours), has no active metabolites, and distributes preferentially to cardiac and renal tissue relative to the kidney-predominant distribution of steroidal MR antagonists [26, 27, 31].

Clinical evidence: Two pivotal Phase 3 trials in diabetic kidney disease have established finerenone: FIDELIO-DKD (5,734 patients; primary renal composite endpoint reduced by 18 percent, hazard ratio 0.82, $p = 0.001$) and FIGARO-DKD (7,437

patients; primary cardiovascular composite endpoint reduced by 13 percent, hazard ratio 0.87, $p = 0.03$) [26, 27]. The FINEARTS-HF trial (2024) studied finerenone in heart failure with preserved or mildly reduced ejection fraction.

Novelty: High. Finerenone is the first non-steroidal MR antagonist to achieve regulatory approval (FDA 2021 for diabetic kidney disease) and represents a fundamentally different structural approach to MR antagonism.

Effect size: Moderate in diabetic kidney disease (18 percent renal composite reduction in FIDELIO-DKD, 13 percent cardiovascular composite reduction in FIGARO-DKD). Heart failure outcomes in FINEARTS-HF demonstrated reduction in worsening heart failure events.

Promising potential: High. Finerenone is actively expanding into heart failure indications and represents the leading edge of MR antagonist development. Its renal indication is novel territory not established for eplerenone.

Side-effect profile: Favorable. No sex hormone-related adverse events. Hyperkalemia rates of approximately 14 to 18 percent in FIDELIO-DKD (versus 19 to 24 percent for spironolactone in comparative analyses), though higher than eplerenone in heart failure trials, reflecting the more severe renal impairment in the diabetic kidney disease population [26, 31].

Overall validation: High. Two positive Phase 3 renal outcomes trials and an expanding clinical program in heart failure.

Comparison to eplerenone: Finerenone and eplerenone target the same receptor but differ in structure (non-steroidal versus steroidal), selectivity mechanism (structural novelty versus epoxy-bridge modification), tissue distribution (balanced cardiac/renal versus kidney-predominant), and established indications (diabetic kidney disease versus heart failure and hypertension). Eplerenone has a longer clinical track record in heart failure and post-MI settings with established mortality data. Finerenone has stronger renal evidence and is the agent of choice in diabetic kidney disease.

12.3 Esaxerenone (CS-3150, Minnebro)

Mechanism: Non-steroidal mineralocorticoid receptor antagonist with potency greater than spironolactone at the MR and high selectivity over androgen, progesterone, and glucocorticoid receptors. Esaxerenone is orally bioavailable with a half-

life of approximately 18 to 20 hours, substantially longer than eplerenone (4 to 6 hours) and finerenone (2 to 3 hours) [32].

Clinical evidence: Esaxerenone is approved in Japan for hypertension (2019) and diabetic nephropathy (2021). The ESAX-DN trial demonstrated reduction in albuminuria in patients with type 2 diabetes and microalbuminuria or macroalbuminuria. Cardiovascular outcomes data are limited to post-hoc analyses; no dedicated heart failure outcomes trial has been completed [32].

Novelty: Moderate to high. The compound represents a second non-steroidal MR antagonist after finerenone, with a longer half-life that may offer pharmacokinetic advantages for once-daily dosing.

Effect size: Demonstrated in albuminuria reduction and blood pressure lowering. Cardiovascular mortality data are not available from dedicated outcomes trials.

Promising potential: Moderate. Approved only in Japan. International development has been slower than finerenone, and the compound faces competitive pressure from finerenone in the diabetic kidney disease space.

Side-effect profile: Similar to finerenone in terms of absence of sex hormone-related adverse events. Hyperkalemia risk has been observed, consistent with the MR antagonist class effect [32].

Overall validation: Moderate. Japanese regulatory approval with positive renal biomarker data, but absent international registration and absent cardiovascular outcomes trial data.

Comparison to eplerenone: Esaxerenone has greater MR potency and selectivity than eplerenone through its non-steroidal scaffold, a longer half-life that may improve adherence, and emerging renal evidence. Eplerenone has a substantially larger and more mature clinical evidence base in heart failure (EPHESUS, EMPHASIS-HF) and broader global regulatory approval.

12.4 Canrenone (potassium canrenoate)

Mechanism: Active metabolite of spironolactone. Canrenone is a steroidal MR antagonist that retains significant androgen and progesterone receptor binding, comparable to spironolactone. It is available in some European and Latin American ju-

risdictions as potassium canrenoate for intravenous administration, providing the only parenteral MR antagonist option [33].

Clinical evidence: Limited to observational studies and small interventional studies. No large randomized cardiovascular outcomes trials have been conducted with canrenone as the primary study drug. The compound is used clinically as an intravenous MR antagonist in acute heart failure decompensation and in the peri-operative setting in jurisdictions where it is available [33].

Novelty: Low. Canrenone is a metabolite of spironolactone and shares its pharmacological liabilities.

Effect size: Not established in dedicated outcomes trials. Clinical effects are inferred from the spironolactone literature.

Promising potential: Low. The compound is unlikely to undergo dedicated outcomes trial development given the availability of spironolactone (oral), eplerenone (oral, selective), and finerenone (oral, non-steroidal). Its principal clinical niche is parenteral MR antagonism in acute settings.

Side-effect profile: Similar to spironolactone, including gynecomastia, breast pain, and menstrual irregularities. Hyperkalemia risk is comparable to other steroidal MR antagonists [33].

Overall validation: Low. The compound has the longest history of clinical use among MR antagonists (as a spironolactone metabolite) but the weakest independent clinical evidence base.

Comparison to eplerenone: Canrenone and eplerenone are both steroidal MR antagonists, but canrenone lacks the selectivity modifications (epoxy bridge, carbomethoxy substitution) that confer eplerenone's favorable sex hormone-related adverse-event profile. Canrenone's principal advantage is its availability as an intravenous formulation, a gap in eplerenone's product profile.

12.5 Ocedurenone (KBP-5074)

Mechanism: Non-steroidal mineralocorticoid receptor antagonist in clinical development for resistant hypertension and chronic kidney disease. Ocedurenone has high MR potency and selectivity, a long half-life supporting once-daily dosing, and

a pharmacokinetic profile that does not require dose adjustment for renal impairment [34].

Clinical evidence: The BLOCK-CKD trial (Phase 2, 2021) studied ocedurenone in patients with uncontrolled hypertension and advanced chronic kidney disease (eGFR 15 to 30 mL/min/1.73 m²), a population in which eplerenone and spironolactone are contraindicated or used with extreme caution due to hyperkalemia risk. Ocedurenone demonstrated significant blood pressure reduction and a manageable hyperkalemia profile in this high-risk population [34].

Novelty: High. Ocedurenone targets a patient population (advanced CKD with uncontrolled hypertension) that is currently underserved by existing MR antagonists.

Effect size: Blood pressure reduction in the BLOCK-CKD trial was clinically significant. Cardiovascular and renal outcomes data from Phase 3 trials are not yet available.

Promising potential: Moderate to high. The compound addresses a genuine unmet need (MR antagonism in advanced CKD). Phase 3 development (CLARION-CKD trial) is ongoing. Regulatory approval has not been achieved.

Side-effect profile: Hyperkalemia rates in BLOCK-CKD were lower than expected for the advanced CKD population, though the small sample size limits interpretation. No sex hormone-related adverse events, consistent with the non-steroidal class [34].

Overall validation: Low to moderate. Phase 2 data in a high-risk population with an unmet need. Phase 3 outcomes data are pending.

Comparison to eplerenone: Ocedurenone targets a population in which eplerenone is contraindicated or high-risk (advanced CKD, eGFR 15 to 30). The two compounds are not directly competitive in the same patient population. Eplerenone has the established evidence base in heart failure and mild-to-moderate renal impairment; ocedurenone may extend MR antagonism to the advanced CKD population if Phase 3 data are positive.

12.6 Comparator summary

The five comparator compounds span two structural classes (steroidal: spironolactone, canrenone; non-steroidal: finerenone, esaxerenone, ocedurenone) and three clinical positioning strategies (established heart failure: spironolactone; diabetic kidney disease: finerenone, esaxerenone; advanced CKD/resistant hypertension: ocedurenone).

Eplerenone occupies a distinct position in this landscape: it is the only steroidal MR antagonist with clinically meaningful selectivity over sex hormone receptors, the only MR antagonist with dedicated positive cardiovascular outcomes trials in both the post-MI (EPHESUS) and mild heart failure (EMPHASIS-HF) populations, and the compound with the most extensive global regulatory approval for heart failure indications after spironolactone. Its principal limitation relative to the non-steroidal agents is lower MR potency (requiring higher doses for equivalent blockade), CYP3A4-dependent metabolism creating drug-drug interaction potential, and the absence of a renal outcomes trial to match the finerenone FIDELIO-DKD and FIGARO-DKD results.

The ongoing evolution of the MR antagonist class, from the non-selective first-generation agent (spironolactone) through the selective steroidal second-generation agent (eplerenone) to the non-steroidal third-generation agents (finerenone, esaxerenone, ocedurenone), represents a progressive refinement of receptor selectivity, tissue distribution, and indication-specific evidence. Eplerenone remains the established standard in heart failure with reduced ejection fraction and in post-myocardial infarction left ventricular dysfunction, a position supported by guideline-recommended quadruple therapy across all major cardiovascular societies.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Eplerenone is approved by the United States Food and Drug Administration for hypertension and for heart failure with left ventricular dysfunction following acute myocardial infarction. The compound is also approved in the European Union, Japan, and multiple additional jurisdictions. Investigators should consult their local regulatory authority and institutional review board before any human research application.