Spironolactone

Essential medicine status

Section: 12. Cardiovascular medicines > 12.4. Medicines used in heart failure

ATC codes: C03DA01

Indication	Heart failure ICD11 code: BD0Z
INN	Spironolactone
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid: 25 mg
EML status history	First added in 2013 (TRS 985)
Sex	All
Age	Adolescents and adults
Therapeutic equivalence	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Spironolactone
DrugBank	Spironolactone

Summary of evidence and Expert Committee recommendations

An application was submitted for aldosterone antagonists to be added as a therapeutic class (with spironolactone as the representative) to Section 12.4 of the EML. Spironolactone has been in the EML since 1983 as a potassium-sparing diuretic. Three clinical trials were presented as evidence for efficacy in the application. The first was the Randomized Aldactone Evaluation Study (RALES, 1999), which demonstrated a significant benefit with the addition of spironolactone to the standard therapy of an angiotensin-converting-enzyme (ACE) inhibitor and a loop diuretic in patients with severe heart failure. This randomized, double-blinded, placebo-controlled trial assessed the efficacy of spironolactone (25 mg) in 1663 patients in 195 centres in 15 countries. Patients included in the trial had New York Heart Association (NYHA) class IV heart failure within the previous six months, NYHA class III or IV heart failure at the time of enrolment, and a left ventricular ejection fraction (LVEF) of no more than 35%. The trial was stopped early after a mean follow-up period of 24 months due to an interim analysis showing that spironolactone was superior to placebo. The trial found a 30% reduction in overall mortality (hazard ratio, HR = 0.70, 95% CI: 0.60–0.82), a 35% reduction in hospitalization (HR = 0.65, 95% CI: 0.54–0.77), and significant improvement in heart failure symptoms based on the NYHA functional class ($P < 0.001$) in the treatment group. The number needed to treat (NNT) to prevent one death over 24 months was 8.8 (1). The second clinical trial was the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which evaluated the effectiveness of eplerenone (25 mg initial dose, titrated to a maximum of 50 mg) in patients with post-myocardial infarction left ventricular systolic dysfunction (left ventricular ejection fraction (LVEF) ≤ 40%) in a randomized, double-blinded, placebo-controlled trial. Eplerenone reduced overall mortality by 15% (HR = 0.85, 95% CI: 0.75–0.96) and cardiovascular disease-specific mortality by 17% (HR = 0.83, 95% CI: 0.72–0.94) when compared with placebo over a mean follow-up of 16 months (2). The third trial was the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), a randomized, double-blinded, placebo-controlled study that also showed that eplerenone was effective in patients with left ventricular systolic dysfunction (EF < 35%) and mild symptoms (NYHA class II). The trial was also stopped early because of a significant decrease in deaths from cardiovascular causes (HR = 0.76, 95% CI: 0.61–0.94) and a decrease in hospitalization from heart failure (HR = 0.58, 95% CI: 0.47–0.70) in the eplerenone treatment group (3). Spironolactone is

associated with an increased risk of gynaecomastia, which may not be as frequent with eplerenone. However, both are associated with an increased risk of hyperkalaemia, which may be worse with eplerenone. Both products would require potassium concentrations to be monitored to ensure safe use. The most recent systematic review concluded that eplerenone was similar to older, less expensive aldosterone antagonists, but hyperkalaemia may be more frequent with epleronone whereas gynaecomastia was more frequent with the older aldosterone antagonists (4). Other systematic reviews have confirmed the decrease in mortality with aldosterone antagonists (5). There are no direct comparative studies of spironolactone and eplerenone. Spironolactone is widely available and inexpensive. Eplerenone is substantially more expensive. Several cost–effectiveness studies from high-income countries show that spironolactone, compared with placebo as an add-on therapy in heart failure patients already treated with ACE-inhibitors and beta-blockers, is cost effective under most assumptions. The Heart Failure Society of America Guidelines Committee recommends: “Until such time as the effectiveness of these two drugs (spironolactone and epleronone) in several different patient groups is compared in a well-designed clinical trial, it seems most reasonable for the clinical use of these agents to be consistent with their use in clinical trials. If cost or insurance reimbursement is an issue, as it will be for many, a reasonable choice is to substitute spironolactone” (6). The Expert Committee recommended the expansion of the indication for spironolactone for heart failure (by listing in Section 12.4, as part of the core list), without a square box because of the current price differential between spironolactone and eplerenone as the other main aldosterone antagonist and possible significant differences in safety profile with respect to hyperkalaemia. No change was made to the EMLc since additional data would be needed to justify inclusion for this patient group, in which the etiology of heart failure is very different. References: 1. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al.; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341(10):709-7. http://dx.doi.org/10.1056/NEJM199909023411001 PMID:10471456 2. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al.; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309-21. http://dx.doi.org/10.1056/NEJMoa030207 PMID:12668699 3. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al.; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21. http://dx.doi.org/10.1056/NEJMoa1009492 PMID:21073363 4. Chatterjee S, Moeller C, Shah N, Bolorunduro O, Lichstein E, Moskovits N, et al. Eplerenone is not superior to older and less expensive aldosterone antagonists. Am J Med. 2012;125(8):817-25. http://dx.doi.org/10.1016/j.amjmed.2011.12.018 PMID:22840667 5. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. Eur Heart J. 2009;30(4):469-77. http://dx.doi.org/10.1093/eurheartj/ehn543 PMID:19066207 6. Butler J, Ezekowitz JA, Collins SP, Givertz MM, Teerlink JR, Walsh MN, et al.; Heart Failure Society of America Guidelines Committee. Update on aldosterone antagonists use in heart failure with reduced left ventricular ejection fraction. J Card Fail. 2012;18(4):265-81. http://dx.doi.org/10.1016/j.cardfail.2012.02.005 PMID:22464767