

# NEWBORN USE ONLY

## Spironolactone

2016

<b>Alert</b>	Spironolactone is a potassium-sparing diuretic and concomitant intake of potassium or ACE inhibitors may lead to hyperkalemia.
<b>Indication</b>	Diuretic primarily prescribed for its potassium-sparing effect. For heart failure, in conjunction with furosemide. For chronic lung disease, in conjunction with a thiazide diuretic. Bartter syndrome and Gitelman Syndrome.
<b>Action</b>	Spironolactone is a synthetic steroid that acts as a competitive aldosterone receptor antagonist, so inhibits sodium reabsorption and spares potassium. It is a weak diuretic. It also inhibits the interaction between dihydrotestosterone and the intracellular androgen receptor resulting in moderate antiandrogenic activity..
<b>Drug Type</b>	Non-selective mineralocorticoid receptor antagonist.
<b>Trade Name</b>	Aldactone; Spiractin
<b>Presentation</b>	Oral suspension prepared in pharmacy. 2.5 mg/mL; 5 mg/mL.
<b>Dosage / Interval</b>	1–3 mg/kg/dose 24 hourly. Dose can be divided into different intervals.
<b>Maximum daily dose</b>	3 mg/kg/day
<b>Route</b>	Oral
<b>Preparation/Dilution</b>	Oral suspension.
<b>Administration</b>	Administer undiluted with feeds.
<b>Monitoring</b>	Serum potassium at regular intervals.
<b>Contraindications</b>	Hyperkalaemia. Significant renal impairment. Anuria. Adrenal insufficiency.
<b>Precautions</b>	Use with caution in infants with renal or hepatic impairment. Monitor more frequently if infant is also given potassium.
<b>Drug Interactions</b>	Spironolactone increases the effects of ACE inhibitors (leading to hyperkalemia), digoxin and sotalol.
<b>Adverse Reactions</b>	Hyperkalaemia and metabolic acidosis. Antiandrogenic effects include reduced hirsutism and gynecomastia. There is one case report of an ovarian cyst in a neonate on spironolactone. Spironolactone interferes with 17-hydroxyprogesterone measurement, which is used to screen neonates for congenital adrenal hyperplasia. Reduces clearance of digoxin.
<b>Compatibility</b>	N/A
<b>Incompatibility</b>	N/A
<b>Stability</b>	Biochemical stability when stored in solution for 1 month. <sup>1</sup>
<b>Storage</b>	Store below 25°C.
<b>Special Comments</b>	Pharmacokinetics not studied in infants. Absorption increased by food. Metabolised to active metabolites 7 $\alpha$ -methylspironolactone and canrenone which are extensively bound to plasma protein at therapeutic concentrations and have extended half-lives.
<b>Evidence summary</b>	<b>Efficacy:</b> <b>In preterm infants &gt; 3 weeks of age with CLD:</b> Acute and chronic administration of thiazide diuretic and spironolactone improved pulmonary mechanics. <sup>2</sup> A single study showed thiazide and spironolactone decreased the risk of death in infants who did not have access to corticosteroids, bronchodilators or aminophylline. <sup>3</sup> (LOE I, GOR C) Trials used spironolactone doses from 3 to 4 mg/kg/day. <b>Heart failure:</b> Spironolactone resulted in short-term improvement in heart failure secondary to congenital heart disease compared to potassium supplementation in infants treated with digoxin and a thiazide diuretic. <sup>4</sup> (LOE II GOR C) In adults with heart failure, the addition of aldosterone antagonists reduced mortality, hospitalisation rate, and hypokalaemia but increased creatinine and occurrence of hyperkalaemia. <sup>5,6</sup> (LOE 1/adults GOR C)

	<p><b>Bartter syndrome and Gitelman syndrome:</b> Spirolactone has been used to maintain serum potassium in patients with Bartter syndrome and Gitelman syndrome.<sup>7</sup></p> <p><b>Pharmacokinetics and pharmacodynamics:</b> Spirolactone is a non-selective mineralocorticoid receptor antagonist with moderate affinity for both progesterone and androgen receptors. Pharmacokinetics and pharmacodynamics have not been evaluated in newborn infants. In adults, absorption is estimated to be 80–90%. The onset of action for spiroolactone is typically very slow, with a peak response sometimes occurring 48 hours or more after the first dose. Spirolactone is rapidly metabolised hepatically into a number of metabolites. The predominant metabolite, 7<math>\alpha</math>-methylspiroolactone, accounts for around 80% of the K<sup>+</sup>-sparing effect of spiroolactone. Spirolactone (88%) and its canrenone metabolite (99%) are extensively bound to plasma protein at therapeutic concentrations. In normal volunteers, the mean t<sub>1/2</sub> of spiroolactone, canrenone, 7<math>\alpha</math>-TMS and 6<math>\beta</math>-hydroxy-7<math>\alpha</math>-TMS were 1.4, 16.5, 13.8 and 15 hours, respectively. In cirrhotic patients, the t<sub>1/2</sub> of spiroolactone and its metabolites are increased. The pharmacokinetics of spiroolactone and its metabolites have not been specifically studied in the setting of renal insufficiency or end-stage renal disease.<sup>8,9</sup></p> <p><b>Safety:</b> Preterm infants receiving hydrochlorothiazide in combination with spiroolactone may have an increased need for sodium and potassium supplementation.<sup>3</sup> (LOE II GOR B) The addition of spiroolactone to a thiazide diuretic did not reduce the requirement for supplemental electrolytes over 2 weeks in a small trial.<sup>10</sup> (LOE II GOR C) Use of spiroolactone in adults increases creatinine and the incidence of hyperkalaemia.<sup>5</sup> (LOE I GOR C) Spirolactone reduced digoxin clearance in infants.<sup>11</sup> (LOE IV GOR C)</p>
<p><b>References</b></p>	<ol style="list-style-type: none"> <li>1. Mathur LK, Wickman A. Stability of extemporaneously compounded spiroolactone suspensions. <i>Am J Hosp Pharm.</i> 1989;46:2040-2.</li> <li>2. Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. <i>Cochrane Database Syst Rev.</i> 2011:CD001817.</li> <li>3. Albersheim SG, Solimano AJ, Sharma AK, Smyth JA, Rotschild A, Wood BJ, Sheps SB. Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. <i>J Pediatr.</i> 1989;115:615-20.</li> <li>4. Hobbins SM, Fowler RS, Rowe RD, Korey AG. Spirolactone therapy in infants with congestive heart failure secondary to congenital heart disease. <i>Arch Dis Child.</i> 1981;56:934-8.</li> <li>5. Hu LJ, Chen YQ, Deng SB, Du JL, She Q. Additional use of an aldosterone antagonist in patients with mild to moderate chronic heart failure: a systematic review and meta-analysis. <i>Br J Clin Pharmacol.</i> 2013;75:1202-12.</li> <li>6. Anonymous. Effectiveness of spiroolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). <i>Am J Cardiol.</i> 1996;78:902-7.</li> <li>7. Fremont OT, Chan JC. Understanding Bartter syndrome and Gitelman syndrome. <i>World J Pediatr.</i> 2012;8:25-30.</li> <li>8. Sica DA. Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. <i>Heart Fail Rev.</i> 2005;10:23-9.</li> <li>9. Karim A. Spirolactone: disposition, metabolism, pharmacodynamics, and bioavailability. <i>Drug Metab Rev.</i> 1978;8:151-88.</li> <li>10. Hoffman DJ, Gerdes JS, Abbasi S. Pulmonary function and electrolyte balance following spiroolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled, randomized trial. <i>J Perinatol.</i> 2000;20:41-5.</li> <li>11. Suematsu F, Minemoto M, Yukawa E, Higuchi S. Population analysis for the optimization of digoxin treatment in Japanese paediatric patients. <i>J Clin Pharm Ther.</i> 1999;24:203-8.</li> </ol>

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<b>Original version Date: 18/07/2016</b>	<b>Author: NMF Consensus Group</b>
<b>Current Version number: 1</b>	<b>Current Version Date: 18/07/2016</b>
<b>Risk Rating: Medium</b>	<b>Due for Review: 18/07/2019</b>
<b>Approval by: As per Local policy</b>	<b>Approval Date: 4/8/16</b>