

## DORSET CARDIOLOGY WORKING GROUP GUIDELINE FOR CALCIUM CHANNEL BLOCKERS IN HYPERTENSION

<p><b>SUMMARY</b></p> <p><b>The pan-Dorset cardiology working group continues to recommend the use of amlodipine (a third generation dihydropyridine calcium-channel blocker) as first choice calcium channel blocker on the pan-Dorset formulary for hypertension.</b></p> <p>Lercanidipine is second choice, lacidipine third choice and felodipine is fourth choice. This is due to preferable side effect profiles in terms of ankle oedema and relative costs of the preparations.</p> <p>Note: where angina is the primary indication or is a co-morbidity prescribers must check against the specific product characteristics (SPC) for an individual drug to confirm this is a licensed indication. N.B. Lacidipine and lercanidipine are only licensed for use in hypertension.</p>	
<p><b>REVIEW BACKGROUND</b></p>	<ul style="list-style-type: none"> <li>• Chapter 02.06.02 CCBs section of the Formulary has undergone an evidence-based review. A comprehensive literature search was carried out on NHS Evidence, Medline, EMBASE, Cochrane Database, and UK Duets. This was for recent reviews or meta-analyses on calcium channel blockers from 2009 onwards (comparative efficacy and side effects) and randomised controlled trials (RCTs).</li> <li>• Very little good quality evidence exists. No reviews, meta-analyses or RCTs were found covering all calcium channel blockers currently on the formulary. Another limitation was difficulty obtaining full text original papers for some of the references therefore having to use those from more obscure journals instead. Some discrepancies exist between classification of generations of dihydropyridine CCBs, depending upon the year of publication of the reference/authors' interpretation.</li> </ul>
<p><b>OVERVIEW OF CALCIUM CHANNEL BLOCKERS IN HYPERTENSION</b></p>	<ul style="list-style-type: none"> <li>• Dihydropyridine (DHP) CCBs tend to be more potent vasodilators than non-dihydropyridine (non-DHP) CCBs (diltiazem, verapamil), but the latter have greater inotropic effects. Both have a similar capacity to lower blood pressure (BP). Non-DHPs appear advantageous in managing patients with chronic kidney disease and diabetic nephropathy.<sup>5</sup></li> <li>• Four generations of DHPs are available. The first generation, nicardipine and nifedipine have proven efficacy in hypertension. Due to short duration and rapid onset of vasodilator action they are more likely to have adverse effects. Second generation slow release and short acting preparations like benidipine and efonidipine have better BP control and reduction in some adverse effects. The third generation DHPs amlodipine and azelidipine (and felodipine) exhibit more stable pharmacokinetics, are less cardio-selective so are well tolerated in patients with heart failure. The fourth generation highly lipophilic DHPs lercanidipine and lacidipine provide stable activity, reduction in adverse effects and broad therapeutic spectrum, especially in myocardial ischaemia and potentially congestive heart failure.<sup>5</sup></li> </ul>

<p><b>RELEVANT NICE GUIDANCE</b></p>	<p>NICE CG 127: Hypertension (August 2011, updates of CG 18 and CG34).</p> <ul style="list-style-type: none"> <li>Offer step 1 antihypertensive treatment with a Calcium Channel Blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. If a CCB is not suitable, for example due to oedema or intolerance or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. [new 2011].<sup>6</sup></li> </ul> <p>Offer step 2 treatment if blood pressure is not controlled by step 1 treatment, offer step 2 treatment with a CCB in combination with either an ACE inhibitor or an ARB<sup>[6]</sup>. [new 2011]</p> <p>(No specific CCB is recommended in CG 127, also due for review September 2015.)</p>
<p><b>PROPOSED FORMULARY STATUS OF CCBs IN HYPERTENSION</b></p>	<ul style="list-style-type: none"> <li>Amlodipine tablets: <b>GREEN, first choice</b> (interaction with simvastatin – risk of myopathy with high-dose simvastatin. Max dose of simvastatin 20mg/day with amlodipine. MHRA DSU 2012, vol 6, issue 1: S1.) <i>(No change)</i></li> <li>Lercanidipine <b>GREEN, second choice</b></li> <li>Lacidipine <b>GREEN, third choice</b></li> <li>Felodipine MR tablets: <b>GREEN, fourth choice.</b></li> <li><b>Non-formulary:</b> isradipine, nicardipine, nisoldipine, diltiazem branded products, amlodipine and valsartan combination product.</li> </ul>
<p><b>PBR STATUS</b></p>	<p>All included.</p>
<p><b>COMMISSIONING IMPLICATIONS</b></p>	<p>Substantial savings potentially available, by using the least costly fourth generation CCB as the alternative prescribing option. Lercanidipine has a preferential side effect profile, interactions profile and similar efficacy to other DHP CCBs.</p>
<p><b>RELEVANT CLINICAL COMMISSIONING PROGRAMME</b></p>	<p>Cardiovascular Disease (CVD) Stroke and Diabetes: included as part of the discussions between local clinicians and commissioners of NICE CG 127 and other available evidence.</p>
<p><b>PATIENT PATHWAY IMPLICATIONS</b></p>	<p>The proposed change to formulary status of lercanidipine will be suitable for a substantial number of patients currently taking felodipine.</p>
<p><b>SUMMARY OF EVIDENCE TO SUPPORT FORMULARY STATUS</b></p>	<p>From the available evidence on safety, tolerability and efficacy of CCBs, the proposal is to change the alternative prescribing option to:</p> <ul style="list-style-type: none"> <li>second choice: lercanidipine (fourth generation lipophilic DHP CCB)</li> <li>third choice: lacidipine (fourth generation lipophilic DHP CCB)</li> <li>fourth choice: felodipine (third generation DHP CCB)</li> </ul> <p><b>Side-effects:</b></p> <ul style="list-style-type: none"> <li>Peripheral oedema including ankle oedema, is a recognized adverse effect of the CCBs. Ankle oedema can range from being mild to severely affecting quality of life. The risk of developing oedema whilst using CCBs appears to be higher in women, older patients, those with heart failure, upright postures (and those in warm environments) which may limit their usefulness. Unlike peripheral oedema caused by fluid</li> </ul>

<p><b>SUMMARY OF EVIDENCE TO SUPPORT FORMULARY STATUS</b></p>	<p>retention, CCB-induced oedema appears to be due to redistribution of fluid from capillaries to interstitial spaces. So it is unaffected by diuretics, occurring despite CCBs possessing inherent diuretic properties. The incidence of ankle oedema appears more frequent in DHP CCBs (reports ranging from 1-15%). Although the more membranophilic (lipophilic) DHPs lercanidipine and lacidipine may have a lower incidence of ankle oedema (uncommon and common respectively), than nifedipine (common) or amlodipine (common) or felodipine (very common). Ankle oedema appears to be dose related. Incidence may be &gt;80% in patients taking long-term, high dose DHPs. While longer-acting CCBs appear to have fewer adverse effects (flushing, headache, palpitations) this doesn't seem the case with ankle oedema.<sup>1</sup></p> <ul style="list-style-type: none"> <li>• Isradipine (another 4<sup>th</sup> generation DHP) is proposed to remain non-formulary due to a relatively high incidence of ankle oedema (very common) compared to lercanidipine (uncommon).<sup>1</sup> Also 28 days treatment of lercanidipine costs far less than isradipine.<sup>2</sup></li> <li>• No formulary changes are recommended for diltiazem and verapamil. Diltiazem is effective in most forms of angina and the longer-acting formulation is also used in hypertension. Verapamil is used for the treatment of angina, hypertension and arrhythmias.<sup>7</sup> Some post-marketing surveillance data has reported a reduced incidence of ankle oedema in patients treated with diltiazem, compared to other CCBs.<sup>1</sup></li> <li>• A meta-analysis of 106 studies concluded that the incidence of peripheral oedema and patient withdrawal due to oedema, progressively increase with duration of therapy up to 6 months. Over the long-term, more than 5% of patients discontinued CCBs because of this adverse effect. The incidence of peripheral oedema was found to be higher for traditional DHPs and lower for the newer lipophilic DHPs (lacidipine and lercanidipine) also non-DHPs.<sup>8</sup></li> <li>• A small, prospective, open-label single-centre study with 58 patients concluded that switching to another DHP CCB may be a solution when intolerance develops to the current DHP CCB (due to pedal/ankle oedema). Patients on amlodipine or nifedipine GITS initially, switched to felodipine or lacidipine. The authors state that comparison of these two drugs with respect to oedema rates is beyond the scope of this study. Oedema is one of the most important reasons for dose reduction or discontinuation of DHP CCBs and can cause misdiagnosis of heart failure, or venous insufficiency leading to unnecessary tests. Study limitations: small study, physical examination only of oedema, longer follow-up required as it can develop many years after therapy initiation.<sup>9</sup></li> <li>• From manufacturers' Summary of Product Characteristics (SPCs) lercanidipine and lacidipine have a similar list of interactions to felodipine. Differences include: lercanidipine and lacidipine plasma levels may be increased by doses of cimetidine &gt;800mg daily.</li> </ul>
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<p><b>SUMMARY OF EVIDENCE TO SUPPORT FORMULARY STATUS</b></p>	<p>Concomitant use of lacidipine and corticoids or tetracosactide might decrease antihypertensive effect. Caution should be exercised when lercanidipine is co-prescribed with other CYP3A4 substrates like terfenadine, astemizole, Class III antiarrhythmic drugs such as amiodarone, quinidine.<sup>4,10,11</sup></p> <p><b>Side effects/efficacy:</b></p> <ul style="list-style-type: none"> <li>• A meta-analysis of 8 RCTs assessed the relative risk of DHP CCB adverse events with lercanidipine versus older DHP CCBs and versus the other lipophilic DHP CCBs. First generation DHPs: amlodipine, felodipine and nifedipine. Second generation lipophilic DHPs: lacidipine and manidipine. Efficacy outcomes for lowering BP did not differ statistically between lercanidipine and either generation of medications. Compared with the first generation, lercanidipine was associated with a reduced risk of peripheral oedema but not flushing or headache. There was no statistical difference between adverse effects with lercanidipine and the other second generation drugs. Study participants were less likely to withdraw from the RCTs because of peripheral oedema or other adverse events when treated with lercanidipine rather than a first generation DHP, but not with other second generation DHPs (funded by Solvay Pharmaceuticals Australia).<sup>12</sup></li> <li>• A Centre for Reviews and Dissemination (CRD) commentary on the above meta-analysis of 8 RCTs comparing the tolerability of lercanidipine with other DHP CCBs stated: treatment duration varied (8 to 104 weeks), most RCTs excluded patients with clinically relevant renal or liver function impairment, all RCTs excluded patients with major CVD. The authors used relevant criteria to examine study quality taking steps to minimise biases and errors in the review process. Statistical heterogeneity was assessed and appropriate methods used to pool results. In view of the limited quality of included studies, a degree of caution might be required in interpreting the authors' conclusions. The authors stated findings from their review may have implications for patient persistence and adherence to treatment in practice when prescribing CCBs for the treatment of hypertension. The authors did not state any implications for research.<sup>13</sup></li> <li>• A systematic review and meta-analysis of 24 studies investigated effects of T-type CCBs against kidney damage in comparison to T-type CCBs or renin-angiotensin system (RAS) antagonists. It concluded that T-type CCBs (benidipine, efonidipine and nilvadipine) are more effective than L-type CCBs (amlodipine, nifedipine) in the protection of renal function, but did not differ from RAS antagonists. Although the proteinuria inhibitory effect of RAS antagonists was absolutely superior to T-type CCBs.<sup>14</sup></li> <li>• A recently developed CCB, cilnidipine blocks L-type and N-type calcium channels, which suppresses the sympathetic nervous system and the renin-angiotensin-aldosterone system. It seems suitable for the various</li> </ul>
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<p><b>SUMMARY OF EVIDENCE TO SUPPORT FORMULARY STATUS</b></p>	<p>types of complications of hypertension.<sup>5</sup> All current formulary and non-formulary CCBs are L-type calcium channel blockers.</p> <p><b>Interactions:</b></p> <ul style="list-style-type: none"> <li>• The interactions between DHP-CCBs and statins have not all been studied in humans either from a pharmacokinetic, clinical perspective or in terms of strength. So further study is needed. From the current data atorvastatin appears to be a safer CYP3A4-statin for comedication with DHP-CCBs.<sup>3</sup></li> <li>• Monitoring is still required when prescribing a lacidipine-simvastatin combination, even though the therapeutic window for simvastatin is not exceeded. The manufacturer recommends taking lacidipine in the morning and simvastatin in the evening. Lercanidipine 20mg with 40mg simvastatin increased the bioavailability of simvastatin by 56% and its active metabolite <math>\beta</math>-hydroxy acid by 28%. The manufacturer recommends taking lercanidipine in the morning and simvastatin in the evening.<sup>3</sup></li> <li>• Refer to section 4.5 of SPCs for CCBs for further details of specific interactions, available at <a href="http://www.medicines.org.uk">www.medicines.org.uk</a></li> </ul>
<p><b>REFERENCES</b></p>	<ol style="list-style-type: none"> <li>1. UKMi Medicines Q&amp;A 322.2. May 2013. What are the reported incidences of ankle oedema with different calcium channel blockers? <a href="http://www.evidence.nhs.uk">www.evidence.nhs.uk</a> accessed 20.01.15</li> <li>2. The January 2015 electronic Drug Tariff. NHSSBSA. Accessed 20.01.15 <a href="http://www.ppa.org.uk/ppa/edt_intro.htm">www.ppa.org.uk/ppa/edt_intro.htm</a></li> <li>3. Zhou YT, Yu LS, Zeng S et al. Pharmacokinetic drug-drug interactions between 1,4-dihydropyridine calcium channel blockers and statins: factors determining interaction strength and relevant clinical risk management. Therapeutics and Clinical Risk Management 2014;10: 17-26.</li> <li>4. Summary of Product Characteristics: Lercanidipine 20mg tablets. Recordati Pharmaceuticals Limited. <a href="http://www.medicines.org.uk">www.medicines.org.uk</a> Accessed 21.01.15</li> <li>5. Chandra K S, Ramesh G. The fourth-generation calcium channel blocker: cilnidipine. Indian Heart J. 2013 65(6): 691-5.</li> <li>6. National Institute for Health and Care Excellence (NICE) Clinical Guideline 127: Hypertension. The clinical management of primary hypertension in adults. August 2011. Update of clinical guidelines 18 and 34.</li> <li>7. Joint Formulary Committee. British National Formulary (BNF). London: BMJ Publishing Group and Royal Pharmaceutical Society. BNF January 2015 app update</li> <li>8. Makani H, Bangalore S, Romero J et al. Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate – a meta-</li> </ol>

<p><b>REFERENCES</b></p>	<p>analysis of randomised trials. <i>Journal of Hypertension</i> 2011;29: 1270-1280.</p> <p>9. Yuksel A, Karaguz A, Ucar O et al. A different dihydropyridine calcium channel blocker in hypertensive patients who developed pedal oedema on dihydropyridine calcium channel blocker therapy. <i>Cumhuriyet Med J</i> 2014;36: 19-24.</p> <p>10. Summary of Product Characteristics: Vasalpha 10mg prolonged release tablets (felodipine). Actavis UK Ltd. <a href="http://www.medicines.org.uk">www.medicines.org.uk</a> Accessed 21.01.15</p> <p>11. Summary of Product Characteristics: Motens® 4mg tablets (lacidipine). GlaxoSmithKline UK Ltd. <a href="http://www.medicines.org.uk">www.medicines.org.uk</a> Accessed 21.01.15</p> <p>12. Makarounas-Kirchmann K, Glover-Koudounas S, Ferrari P. Results of a meta-analysis comparing the tolerability of lercanidipine and other dihydropyridine calcium channel blockers. <i>Clinical Therapeutics</i> 2009;31(8): 1652-1663.</p> <p>13. Database of Abstracts of Reviews of Effects (DARE) produced by the Centre for Reviews and Dissemination (CRD), University of York 2010. Review of results of a meta-analysis comparing the tolerability of lercanidipine and other dihydropyridine calcium channel blockers (Makarounas-Kirchmann et al.) Accession number: 12010000643. <a href="http://www.crd.york.ac.uk">www.crd.york.ac.uk</a> accessed 12.01.15</p> <p>14. Li X, Yang MS. Effects of T-type calcium channel blockers on renal function and aldosterone in patients with hypertension: a systematic review and meta-analysis. <i>PLoS ONE</i> Oct 17 2014;9(10): e109834 <a href="http://www.plosone.org">www.plosone.org</a> accessed 12.01.15</p>
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