Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Calcium Channel Blockers***
-August 2014-

Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the role of calcium channel blockers (CCBs) as part of a larger review of medications used for the treatment of hypertension in the August 2014 meeting. The review evaluated safety and efficacy of CCBs as first-line agents for the treatment of hypertension, including critical evaluation of the current agent's available and potential new agents for addition to the IHS National Core Formulary (NCF). The NPTC also evaluated comparative efficacy and safety of CCBs versus other first-line antihypertensive drug classes. The literature discussed in the review included large database drug class reviews from the Cochrane Library, national guidelines for the treatment of hypertension, and the most current primary literature. The review and discussion led to the removal of verapamil and nifedipine from the NCF. The NPTC retained diltiazem and amlodipine as CCBs on the NCF.

Discussion:
Hypertension has been estimated to cost the United States $93.5 billion annually in medication and health care costs[1]. Patients with hypertension are at an increased risk for cardiovascular disease, such as heart attack and stroke. In 2014, the Eighth Joint National Committee (JNC 8) published updated guidelines for the treatment of hypertension[2]. These guidelines include CCBs as first-line agents for hypertensive patients without chronic kidney disease. The NPTC review compared agents within this class to each other and to antihypertensive medications of other first-line classes, as designated by JNC 8 (angiotensin converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], and thiazide-type diuretics).

There are two main classifications of CCBs: dihydropyridines and non-dihydropyridines[3]. Both classes inhibit L-type calcium channels on cardiac and vascular smooth muscle. The dihydropyridines exhibit greater selectivity for the vasculature leading to potent vasodilation and improved reduction in blood pressure, while the non-dihydropyridines exhibit a negative chronotropic effect that is not seen in dihydropyridines. Agents reviewed include non-dihydropyridines (diltiazem and verapamil) and dihydropyridines (amlodipine, clevidipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine).

Findings:
Efficacy: From the limited comparative literature available, the CCB agents currently available on the NCF are non-inferior to other available CCB agents in terms of anti-hypertensive effects[3,4,5]. CCBs have been shown to be superior to beta blockers in the reduction of cardiovascular events and mortality[6], superior to ARBs in the reduction of heart attacks[6], and superior to ACEIs, ARBs[6], and beta blockers[6,7] in the reduction of strokes. These reviews did not identify which CCB agent was the most effective in achieving these primary endpoints.

Safety: Research on the comparative safety profiles of CCBs is limited to a handful of agents. Common side effects of CCBs include peripheral edema, headache, and flushing[8]. These adverse effects can be attributed more commonly to dihydropyridine CCBs, such as amlodipine and nifedipine[9]. Among the dihydropyridines, studies show the first generation agents such as nifedipine have a higher rate of adverse events than newer, more lipophilic agents such as amlodipine[9,10,11]. Additionally, CCBs are largely metabolized by the CYP3A4 system. This contributes to numerous drug-drug interactions with medications that are inhibitors or inducers of this enzyme, including amiodarone, carbamazepine, clarithromycin, clopidogrel, and simvastatin[8]. Verapamil is a substrate for at least four other CYP450 enzymes and interferes with the p-glycoprotein mediated excretion of many other medications. This may cause verapamil to have more drug-drug interactions than other CCBs. As a class, dihydropyridine CCBs were shown to be more likely than ACEIs, ARBs, and diuretics to contribute to congestive heart failure

exacerbations[6,12]. No specific CCB agent was shown to contribute more highly to this complication when compared to other agents in the class.

Conclusion:
The currently available data suggests no difference in efficacy between agents within the non-dihydropyridine classification or between agents within the dihydropyridine classification of CCBs. The NCF currently has two agents from each of these classifications. However, evidence shows increased risk of adverse events with nifedipine compared to amlodipine and increased drug-drug interactions with verapamil compared to diltiazem. Therefore, the NPTC determined having one non-dihydropyridine (diltiazem) and one dihydropyridine (amlodipine) on the NCF encourages providers to utilize the most effective and safest CCBs when treating patients with hypertension or other FDA-labeled indications.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

1. Centers for Disease Control and Prevention. High blood pressure fact sheet. Accessed at http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_bloodpressure.htm on July 21, 2014.
2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guidelines for the management of high blood pressure in adults, report from the panel members appointed to the Eighth Joint National Committee (JNC8). JAMA. 2014; 311(5): 507-20.
3. McDonagh MS, Eden KB, Peterson K. Drug class review on calcium channel blockers, final report. Oregon Health & Science University, Evidence-Based Practice Center. 2005.
4. Van Der Krogt JP, Brand R, & Dawson EC: Amlodipine versus extended-release felodipine in general practice: a randomized, parallel-group study in patients with mild-to-moderate hypertension. Curr Ther Res 1996; 57:145-158
5. Mounier-Vehier C, Bernaud C, Carre A, et al: Compliance and antihypertensive efficacy of amlodipine compared with nifedipine slow-release. Am J Hypertens 1998; 11:478-486.
6. Chen N, Zhou M, Yang M, Guo J, Zhu C, Yang J, Wang Y, Yang X, He L. Calcium channel blockers versus other classes of drugs for hypertension (Review). Cochrane Lib. 2010. 8: CD003654.
7. Chen GJ, Yang MS. The effects of calcium channel blockers in the prevention of stroke in adults with hypertension: a meta-analysis of data from 273,543 participants in 31 randomized controlled trials. PLoS ONE. 2013. 8(3): e57854.
8. Micromedex Online Reference. Accessed at www.micromedex.com on July 21, 2014.
9. Makani H, Bangalore S, Romero J, Htyte N, Berrios RS, Makwana H, & Messerli FH. Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate–a meta-analysis of randomized trials. Jour Hypertens. 2011; 29(7): 1270-1280.
10. Licciardello G, Privitera A, Calvi V, et al: Amlodipine vs nifedipine: a crossover study of efficacy and tolerability in patients with stable angina pectoris. Clin Drug Invest 1997; 13(suppl 1):119-125.
11. Pandolfo L, Pajes G, Zardi D, et al: Anti-ischaemic efficacy of amlodipine vs nifedipine in the treatment of patients with stable exertional angina. Clin Drug Invest 1997; 13(suppl 1):113-118.
12. Davis BR, Cutler JA, Gordon DJ. Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288.23: 2981-2997.