



**Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Diuretics
-August 2014-**



Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the diuretics class at the August 2014 meeting. The last review of this class occurred two years ago with the addition of chlorthalidone to the National Core Formulary (NCF). However, with the release of JNC 8 it was decided to review the class again to evaluate if any other modifications were necessary. The discussion included clinical, utilization and procurement data for this class of medications. This discussion did not lead to a formulary modification; however it was felt that a formulary brief would be of benefit to IHS providers.

Discussion:

Historically, diuretics have been the mainstay for the treatment of hypertension and the first line agent. Worldwide hydrochlorothiazide (HCTZ) is the most widely prescribed medication for blood pressure.¹ The publishing of JNC 8 reinforced thiazide-type diuretics as being the first line choice for the treatment of hypertension with a review of the most current clinical studies (only RCTs were reviewed by the panel). The following is the recommendation from JNC 8 and is rated a grade B:

Recommendation 6: In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation)

The main difference between JNC 7 and JNC 8 is although thiazide-type diuretics have been shown in studies to have a more potent effect at lowering blood pressure than CCB, ACEI and ARB, these agents can also be used as first line therapy depending on therapeutic necessity. In JNC 7, a thiazide-type diuretic was the lone first initial agent. Additionally, there were no RCTs of good or fair quality comparing aldosterone receptor antagonists (spironolactone) and loop diuretics (furosemide) and therefore are not recommended as first line treatment in hypertension. However, they are effective at lowering blood pressure and can be beneficial as add-on therapy especially in situations with heart failure or edematous conditions. The long term outcomes for these other diuretics for morbidity and mortality prevention are lacking.²

Randomized Controlled Studies:

Two landmark randomized control trials have shown the efficacy of thiazide-type diuretic in cardiovascular disease. They were the ALLHAT and MRFIT. Another trial, HYVET, supports potassium diuretics in the elderly. The ALLHAT was a large study including 42,418 patients and compared traditional antihypertensive medicines with newer classes of antihypertensive agents. The study demonstrated that chlorthalidone is superior at preventing CVD events compared to each of the treatment drugs studied: calcium channel blocker (amlodipine), ACE inhibitor (lisinopril), and alpha-adrenergic blocker (doxazosin).³ The MRFIT trial, which occurred in the 1970s, showed that chlorthalidone had statistically significant reductions in mortality compared to HCTZ.⁴ The HYVET trial focused on elderly patients and demonstrated positive outcomes (reduction in mortality and stroke) with the use of indapamide ER for hypertension. Patients in this trial were 80 years of age and older.⁵

American Society of HTN/International Society of HTN (ASH/ISH):

In January 2014, ASH/ISH had a position paper documenting their recommendations for the treatment of hypertension. The following are their recommendations:

1. Positive clinical outcome benefits (reduction in strokes and cardiovascular events) have been established with chlorthalidone, indapamide and HCTZ.
2. Chlorthalidone is more potent than HCTZ (dose comparison) and has a long duration.
3. Thiazide-type diuretics are more effective when combined with ACEI or ARB, but also effective when combined with CCB and β -blockers (use caution in diabetes patients)⁶

Cochrane Review: Diuretics for Heart Failure:

A Cochrane review was performed in 2012 with the use of diuretics in heart failure. The review included 14 trials with 525 participants, 7 placebo-controlled, and 7 vs. ACEI or digoxin. The largest study (n=202) was 24 weeks in duration. The longest study included was 52 weeks (n=77). Mortality was lower for participants treated with diuretics than for placebo (OR for death: 0.24, 95% CI: 0.07-0.83; P=0.02). Admission for worsening HF (n=169) was reduced in those taking diuretics (OR 0.07; CI: 0.01-0.52; P=0.01). Four trials showed improved exercise capacity in CHF compared to control (n=91). The author's conclusion is that diuretics have not been shown to lower deterioration or improve prognosis in CHF (limitations: small sample size and poor study designs), however, they acknowledged that the common clinical impression is that diuretics do reduce mortality and reduce progression of heart disease. The few studies performed suggest combined results from small heterogeneous studies show evidence that diuretics relieve symptoms, reduce episodes of decompensation and exercise capacity. However, they state weak supporting evidence on overall endpoint mortality. Although large RCTs do not give supportive data, the mainstay to heart failure treatment continues to be potassium sparing diuretics.⁷

Cochrane Review: Blood Pressure Lowering Efficacy, Potassium-Sparing:

Again in 2012, a Cochrane review was performed on potassium-sparing diuretics in hypertension. They specifically evaluated literature for blood pressure lowering efficacy of K-sparing diuretics (that block the epithelial sodium channel-ENaC blockers) for primary HTN. Diuretics in this class are amiloride and triamterene. The search period was 1950-2012 and included blinded RCTs (3-12 weeks). Results revealed no trials found for blood pressure lowering efficacy of ENaC blockers as monotherapy. There were six trials with amiloride or triamterene as secondary drug (low dose). The authors concluded low doses of amiloride and triamterene were not shown to reduce blood pressure and, therefore, ENaC blockers do not have statistically or clinically significant effects of lowering blood pressure at low doses. In the future, RCT studies need to be performed at higher doses to see how effective these agents can be for hypertension.⁸

Cochrane Review: Blood Pressure Lowering Efficacy, Thiazide Monotherapy

In 2014, a Cochrane review examined literature on the blood pressure-lowering efficacy of monotherapy with thiazide diuretics for primary hypertension. The search period was from 1946 to 2014 and included any double-blinded RCT comparing fixed-dose thiazide diuretic monotherapy with placebo for 3-12 weeks in patients with primary hypertension. They reviewed sixty studies that included six different thiazide diuretics (n=11,282). The authors' conclusions were the following:

1. Thiazides have greater effect on systolic BP than diastolic: 4-6 mmHg (greater than 3 mmHg seen in ACEIs, ARBs and renin inhibitors and 2 mmHg in non-selective β -blockers)
2. This review could not estimate ADEs because of incomplete reporting
3. The review demonstrated a dose-related BP lowering effect of HCTZ and did not show that with others⁹

The dose dependent lowering effects are summarized in the following chart: (*33 trials with HCTZ)

Dose	BP Lowering
6.25 mg	4/2 mmHg
12.5 mg	6/3 mmHg
25 mg	8/3 mmHg
50 mg	11/5 mmHg

Cochrane Review: Blood Pressure Lowering Efficacy, Loop Diuretics:

In 2012, a Cochrane review of the blood pressure lowering efficacy of loop diuretics for primary in hypertension was conducted. The purpose was to review double blinded RCTs of at least 3 weeks duration comparing loop diuretics with a placebo in patient with primary hypertension, defined as BP>140/90 mmHg at baseline. Only nine trials evaluating the efficacy of five loop diuretics (furosemide, cicletanine, peretanide, indacrinone and etozolin) were identified (n=460). Results and authors' conclusions were as follows:

1. Baseline BP was 162/103 mmHg; trial duration of 8.8 weeks
2. Best estimate of systolic/diastolic BP lowering efficacy of loop diuretics: 7.9/4.4 mmHg (no CI mentioned)
3. BP-lowering effect of loop diuretics is modest and likely overestimated due to the high risk of bias in the studies included in the review
4. Dosing ranging effects could not be determined
5. No clinically meaningful difference in blood pressure-lowering effect compared to other antihypertensive agents were identified¹⁰

Findings:

Although the role of diuretics, especially thiazide-type, did not change with the recommendations from JNC 8, the data reviewed by the expert panel did affirm that these agents are still to be the first-line agent in the treatment of hypertension because of their unsurpassing ability to lower blood pressure, evidence of reduced mortality and cardiovascular events in RCTs and low cost. Potassium sparing and loop diuretics have shown their efficacy in lowering blood pressure and being useful as adjunct in certain situations. As a result, the discussion with the NPTC members concluded that no changes were necessary on the NCF. Diuretics currently on the NCF include chlorthalidone, HCTZ, furosemide and indapamide.

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](#).

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