Proposed Versions of Draft Labeling

The following are versions of draft labeling for antihypertensive drugs as drafted by various persons. Most were envisioned as preambles to the Clinical Trials section.

Version 1

The objective of treating hypertension is to reduce blood pressure, either systolic alone or systolic and diastolic and in turn reduce rates of cardiovascular morbidity and mortality. A reduction of stroke rates has been the largest and most consistent clinical benefit demonstrated using a variety of antihypertensive agents of differing pharmacologic action. This benefit has been demonstrated in placebo controlled trials of substantial size and duration, using a variety of pharmacologic agents that include diuretics (chlorthalidone, thiazide diuretics, HCTZ+Amiloride), beta blockers, ACE-inhibitors (ramipril), ARB's (losartan), and calcium channel blocker (e.g. nitrendipine). It is difficult to quantify accurately the true efficacy of any single agent as most studies permitted add-on therapy to achieve goal blood pressure.

The magnitude of benefit in terms of cardiovascular morbidity and mortality for outcomes other than stroke (e.g., CHD death, fatal/non-fatal MI, sudden death, etc.) is relatively less pronounced than for stroke but never the less still significant. Recent studies indicate that individual drugs may differ in their effects on endpoints such as congestive heart failure.

The benefit of antihypertensive therapy is greater in patients with greater elevations of blood pressure. This benefit is also present regardless of age. This benefit is seen in patients with other co-morbidities (e.g., diabetes mellitus, hypercholesterolemia, existing CAD). Certain antihypertenisves are less likely to be effective in certain ethnic groups (e.g., RAS inhibitor in Blacks). Also certain antihypertensives are more likely to be preferable in certain settings (e.g., ACE-inhibitors and beta blockers for congestive heart failure; beta blockers and RAS inhibitors for post-MI; RAS inhibitors for diabetes). Selection of a particular agent should be individualized. A large fraction of patients will need more than one drug to reach goal pressure. The specific information available on DRUGNAME as well as studies of drugs in its pharmacologic class appears in the Clinical Studies section.

Version 2

The purpose of treating hypertension is the reduction of rates of stroke, heart attacks, heart failure, death, and renal failure. To date, every placebo-controlled study of substantial size has demonstrated that reduction of blood pressure, systolic alone or systolic and diastolic, leads to reduction of stroke rates (regimens containing high- and low-dose diuretics, reserpine, beta blockers, hydralazine) and many studies have also shown reduced rates of overall mortality and cardiovascular events in patients with and without co-morbidity such as diabetes mellitus, lipid abnormalities, and existing coronary artery disease. Individual drugs differ in their established effects in heart failure and progression of renal function abnormalities, and theycould also differ somewhat in effects on other endpoints, although such differences have not been established, with one exception. High-dose diuretics leading to hypokalemia appear to decrease favorable effects on CV mortality.

Although the choice of drug therapy may affect specific endpoints and will influence adverse effects, the principal goal of treatment is reduction of blood pressure. Current JNC 7 guidelines suggest a goal of 120/80 mmHg (110/70 in diabetics) and there is evidence that lower pressure leads to better outcome. A large fraction of patients will need more than one drug to reach goal pressure. The specific information available on DRUGNAME as well as studies of drugs in its pharmacologic class appears in the Clinical Studies section.

Version 3

A wide variety of anti-hypertensive drugs with very different pharmacologic actions have been studied in placebo-controlled outcome trials in patients with hypertension, and all of the drugs studied have been shown to reduce the occurrence of cerebrovascular, cardiovascular, and renal adverse outcomes. This benefit of antihypertensive therapy appears to be related to the lowering of BP rather than to any specific class of drugs, and has generally been greater in patients with greater elevations of blood pressure. This benefit also appears to extend to patients with isolated diastolic or systolic hypertension, and is independent of the patient's age and gender. Benefit has generally been greater in patients with greater elevations.

Many other antihypertensive drugs have not been studied in placebo-controlled trials measuring these adverse events, but have been studied in randomized, placebo-controlled outcome trials in other clinical settings (*e.g.*, heart failure, post-myocardial infarction). In these settings, the results have been either favorable (beta-blockers and ACEIs in CHF and after MI) or without evidence of harm (prazocin and amlodipine in CHF, verapamil and diltiazem post-MI). Given such neutral or favorable

effects in vulnerable populations other than patients with hypertension it would be expected that those agents, even though not tested in hypertension outcome studies, would have the usual beneficial effects derived from lowering blood pressure.

Particular populations of hypertensives may benefit from properties of particular agents (*e.g.*, ACEIs and beta blockers in patients with CHF and post-MI, captopril in diabetic renal disease, ramipril in patients at high risk of major cardiovascular events). Other agents may be less efficacious under certain clinical circumstances. For example, the use of short-acting CCBs after MI is not recommended.

Version 4

A wide variety of anti-hypertensive treatments with very different pharmacologic actions, generally used in combinations, have been shown in placebo-controlled trials to reduce hypertension-related cerebrovascular, cardiovascular, and renal adverse outcomes in patients with mild to severe hypertension (DBP 95-125; systolic BP 160 and higher). The benefit of antihypertensive therapy thus appears to be related to the lowering of BP rather than to any specific class of drugs. The effect on stroke has been most consistent (about 40% reduction in risk for a change of 6 mmHg in systolic or diastolic pressure), with a smaller effect on cardiovascular events (about 14% for a change of 6 mmHg in older studies using high-dose diuretics but about 30% in more recent studies using lower diuretic doses and studies avoiding hypokalemia with potassium retaining drugs). There is also a reduced rate of progression of renal disease in treated patients. Benefits appear similar in patients with diastolic BP elevations (over 95 mmHg), generally accompanied by systolic BP elevation, and isolated systolic hypertension alone (SBP >160) and in younger and older populations. Benefit has generally been greater in patients with greater elevations. There are no recognized gender differences in response or outcome.

The aim of drugs therapies for patients with hypertension is the prevention of cerebrovascular, cardiovascular and renal adverse outcomes. Drugs from a wide variety of pharmacologic classes have been shown to reduce the incidence of these events in randomized, placebo-controlled trials: reserpine, hydralazine, diuretics (thiazides and chlorthalidone), beta-blockers (propanolol, metoprolol, atenolol), calcium-channel blockers (nitrendipine) and angiotensin converting enzyme inhibitors (ACEIs). There are no placebo-controlled hypertension outcome studies to date with alpha blockers or angiotensin II antagonists and

none in which an angiotensin converting enzyme inhibitor was the primary treatment. There is no example of a drug that has lowered blood pressure in a placebo-controlled trial that has not also reduced cerebrovascular and cardiovascular adverse events.

Drugs that have been included in successful outcome studies include reserpine, hydralazine, thiazide diuretics, chlorthalidone, propanolol, metoprolol, atenolol, nitrendipine (a dihydropyridine calcium channel blocker) and enalapril. There are no placebo-controlled hypertension outcome studies to date with alpha blockers or angiotensin II antagonists and none in which an angiotensin converting enzyme inhibitor was the primary treatment. In general, different classes of antihypertensive agents have not been distinguishable from others with respect to effects on outcomes in placebo-controlled studies, except that high-dose diuretics (100 mg HCTZ or equivalent) used without effective potassium maintenance, have shown a smaller beneficial effect on cardiovascular outcomes, perhaps because they cause hypokalemia, which increases the risk of sudden death. Direct large studies comparing different therapies have been uncommon but recent studies have suggested that doxazocin is inferior to other treatments with respect to heart failure (but not with respect to stroke or survival). Particular populations of hypertensives may benefit from properties of particular agents. Some antihypertensives, for example, notably some ACEIs and beta blockers, have been shown to be effective in the treatment of congestive heart failure. Captopril has been shown to slow progression of renal disease in diabetics. Beta blockers and calcium channel blockers are effective anti-anginal agents. Ramipril lowers the risk of stroke, MI and death in patients at high risk of those events.

Members of several classes of antihypertensive drugs, including both drugs not studied in large hypertension outcome trials (CCBs, ACEIs) and those that have been studied in such trials (beta blockers) have been studied in large randomized outcome trials in other settings, such as heart failure (several ACEIs, several beta-blockers, prazosin, amlodipine) and after a myocardial infarction (several ACEIs, several beta-blockers, several CCBs) without evidence of harm (prazocin and amlodipine in CHF, verapamil and diltiazem post-MI) or with evidence of benefit (ACEIs and beta-blockers in CHF and after MI). Given such neutral or favorable effects in vulnerable populations, it would therefore be expected that those agents, even though not tested in hypertension outcome studies, would have the usual beneficial effects of lowering blood pressure on outcomes.

Warnings and precautions for all classes need to be observed: verapamil, diltiazem and most CCBs should not be used in patients with heart

failure; immediate-release nifedipine should not be used to treat hypertension or an acute MI.

Version 5

DRUGNAME is indicated for the treatment of { mild | moderate | severe } { to { moderate | severe } } hypertension, to reduce the risk of cardiovascular events, primarily strokes and myocardial infarction. These benefits have been seen with a wide variety of antihypertensive drugs from a wide variety of pharmacological classes { including the class to which this drug principally belongs }. Evidence for risk reduction with DRUGNAME is {not} available.