AN APPLICATION TO RECOMMEND THAT ANGIOTENSIN RECEPTOR BLOCKER BE ADDED TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES AS AN AGENT FOR TREATMENT OF HYPERTENSION, HEART FAILURE, AND CHRONIC KIDNEY DISEASE

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1. Executive Summary

Hypertension is the leading cause of death globally [1], and the burden of hypertension disproportionately afflicts the world’s poorest countries [2]. Tools to control and treat hypertension are therefore essential to prevent premature mortality and morbidity in vulnerable populations.

In 2002, the World Health Organization approved the addition of angiotensin-converting-enzyme inhibitors (ACE-i) to the WHO Essential Medicines list, due to their efficacy as anti-hypertensive medications and their demonstrated efficacy in the treatment of heart failure and chronic kidney disease (CKD), especially in persons with diabetes [3].

However, the adverse effects associated with ACE-I, such as cough, occur in up to 20-50% of select populations [4,5]. Because the incidence of cough is approximately 68% less with ARBs than ACE-I [6], and high-quality evidence suggests their clinical efficacy is comparable [6,7,8,9], ARBs are routinely indicated for the same conditions as ACE-I for patients unable to tolerate the latter due to cough or other toxicities. However, ARBs are not currently listed on the WHO Essential Medicines list.

We therefore propose a square-box addition for ARBs to the WHO Essential Medicines List, with losartan (ATC Code C09CA01) as the exemplar for this drug class, for persons with hypertension, diabetes, or heart failure or who cannot tolerate ACE-I.

2. Name of the focal point in WHO submitting or supporting the application N/A

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4. International Proprietary Name (INN) Losartan

5. Formulation proposed for inclusion see Section 12

6. Listing as individual medicine or representative of therapeutic group Square-
7. Treatment Details

ARBs lower blood pressure by modulating the renin-angiotensin-aldosterone system to block activation of the angiotensin II AT$_1$ receptors, preventing angiotensin II from binding there. The 2013 American College of Cardiology/American Heart Association Guideline for the Management of Heart Failure and the 2016 European Society of Cardiology Guidelines for the Treatment of Acute and Chronic Heart Failure recommend the use of ARBs for those with heart failure and reduced ejection fraction who are ACE inhibitor intolerant to reduce morbidity and mortality [10,11], and the 2013 European Society of Cardiology Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases recommend ARBs for persons with diabetes and hypertension, especially with concomitant coronary artery disease [12], to reduce morbidity and mortality. Renal function and electrolytes should be checked prior to initiation of treatment, after 1-2 weeks of treatment, and 1-2 weeks after final dose titration. ARBs are typically to be used life-long. Starting and target doses of commonly used ARBs are shown in Table 1.

<table>
<thead>
<tr>
<th>Angiotensin Receptor Blocker (ARB)</th>
<th>Starting Dose (mg)</th>
<th>Target Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4-8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>40 mg twice daily</td>
<td>160 mg twice daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>50 mg daily</td>
<td>150 mg daily</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150 mg daily</td>
<td>300 mg daily</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>20 mg daily</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>40 mg daily</td>
<td>80 mg daily</td>
</tr>
</tbody>
</table>

8. Information Supporting Public Health Relevance

Hypertension is the leading risk factor for global burden of disease, accounting for 9.4 million deaths and 7% of global disability-adjusted life years (DALYs) in 2010 (13). Hypertension significantly contributes to risk for many diseases, including coronary heart disease, stroke, chronic kidney disease, and heart failure (14)(15). According to the INTERHEART study, people with hypertension have significantly increased risk of acute myocardial infarction compared to people without hypertension, with an adjusted odds ratio of 1.91 and population attributable risk of 17.9%, regardless of gender, age, or region of the world (16). Hypertension is also major risk factor for heart failure, and is the predominant cause of heart failure in Africa and the Americas (17)(18).

Hypertension is a global problem that is growing, 80 percent of cardiovascular deaths occur in low and middle income countries (19). This is of particular significance as cardiovascular disease (CVD) is the leading cause of death from non-communicable
diseases in the world (19). The number of people in Africa with hypertension is expected to increase 68% from 75 million in 2008 to approximately 125 million in 2025. (18). The number of deaths from CVD rose 12.5% between 2005 and 2015 to 17.9 million.

In addition to CVD, chronic kidney disease, which is tied intrinsically to hypertension as a sequela and cause, has become an increasingly more worrisome contributor to morbidity and mortality worldwide. Death from chronic kidney disease rose by 31.7% from 2005 to 2015, to 1.2 million deaths annually (21). As it is clear that the burden of hypertension contributes directly and significantly to global burden of disease, much benefit can be found in attempting to reduce the severity, incidence, and prevalence of hypertension globally.

The Prospective Urban Rural Epidemiology (PURE) project has contributed greatly to our understanding of the epidemiology and medicine utilization as it pertains to hypertension across the globe. Various studies have revealed very poor rates of patient awareness, treatment, and blood pressure control. For example, one study found that only 46.5% of subjects with hypertension were aware of their diagnosis, and while 87.5% of those were receiving medical treatment, only 32.5% had good blood pressure control (22).

Awareness and treatment parameters were statistically significantly lower in low-income communities as compared to low-middle, high-middle, and high-income communities. This problem also varied by region. In the Middle East PURE study, for example, only about 50% of people with hypertension were aware of their diagnosis, with only 47% of those treated and only 19% with good blood pressure control (23).

The issues of adequate pharmacologic treatment and blood pressure control are intrinsically tied to the availability and affordability of blood pressure medications. One study, which looked at aspirin, beta blockers, angiotensin converting enzyme inhibitors (ACEi), and statins, showed that the availability of all of these medications decreased considerably from high- to low-income countries, while the unaffordability only increased (24). In addition, in low-income and middle-income countries, patients with previous CVD were less likely to use any of the four medications if fewer than four were available, underlining the importance of broad medicine availability in these countries. Specifically, use of ACEi and angiotensin receptor blockers was as low as 5.2% in low-income countries, likely due to medication availability and cost as rates of use were more related to country-level factors the individual-level factors (25).

As mentioned above, ARB’s have a favorable side effect profile compared to that of ACEi. With lower incidence of cough and angioedema, patients that are unable to tolerate ACEi may likely see benefits from an ARB. A meta-analysis of trials comparing ACEi and ARBs for primary hypertension demonstrated an absolute risk reduction of 1.8% of withdrawals due to adverse effects. (7) While at first glance the number may be seemingly small, the large global burden of disease of hypertension of over one billion individuals provides a sizeable population that would benefit from ARB therapy availability.

There is strong evidence that treatment control of hypertension can save both lives and money. A reduction in systolic blood pressure of 5mm Hg in systolic blood pressure has been demonstrated to reduce all cause mortality by 7% and stroke by 14%. (26) In 2009, the global cost of sub-optimal blood pressure control was estimated at $370
billion dollars annually. (27)

9. Review of Benefits and Summary of Comparative Effectiveness

Considerable high-quality data has demonstrated the efficacy of angiotensin converting enzyme inhibitors (ACE-i) for the treatment of hypertension; and secondary prevention after diabetes, heart failure, and myocardial infarction among other conditions [10,11,12]. This impact occurs through multiple pathways, such as reduced sympathetic activity; inhibited release of endothelins; and cytokine modulation associated with inhibition of the renin-angiotensin system [13,14,15]. These medications are low-cost and highly-available in developing countries [16], and are generally well-tolerated, such that their inclusion on the WHO EML was approved in 2002 [3].

However, because ACE-i also inhibit pulmonary kininase activity, they frequently cause cough mediated by bradykinin [4,5]. Angiotensin II receptor blockers (ARBs), because they inhibit the renin-angiotensin system by blocking angiotensin II from binding to the AT1 receptor, are associated with markedly lower incidence of cough [6]. ARBs nonetheless remain as effective as ACE inhibitors for the indications above, as follows:

Hypertension

The efficacy of ARBs and ACE-i in blood pressure control, and consequent prevention of cardiovascular morbidity and mortality, is well-established. A 1999 study by Dickerson et al [17] of the comparative efficacy of ACE-i relative to beta-blockers, calcium-channel blockers, and diuretics for hypertension control in 56 younger (age 21-56) white adults with essential hypertension found significantly greater likelihood of a good response (greater than the mean plus 1 SD of all responses) for ACE-I than the other agents: 16 for ACE-I versus 10, 4, and 4 for B-blockade, calcium-channel blockade, and diuretic respectively (p<0.05); in seven cases, patients were switched from ACE-I to ARB with comparable results [20]. A 2006 systematic review by Matchar et al [6] found no significant difference in blood pressure lowering between ARBs and ACE-I across 61 studies over 40 years. A Cochrane Collaboration systematic review in 2014 by Li et al [7], who examined nine studies with 11,007 participants, found no significant difference between the two categories of agents with respect to total mortality; total cardiovascular events; or cardiovascular mortality. A 2016 systematic review of randomized trials by Bangalore et al in more than 250,000 patients without heart failure [8] confirmed this result, finding no significant difference with respect to all-cause mortality, cardiovascular mortality, and myocardial infarction. Moreover, relative to placebo, ARBs were significantly associated with reduced risk of multiple hypertension sequelae such as heart failure, stroke, and end-stage renal disease [8].

Diabetes

Evidence suggests ARBs and ACE-I may be superior to other antihypertensives in the secondary prevention of cardiovascular events in persons with diabetes [12] because, in
addition to their impact on blood pressure control, these medications address other sequelae of diabetes directly, such as plasma glucose concentration and macroalbuminuria. Alkarouf et al found in 1993 that administration of captopril to 130 patients with type 2 diabetes led to a reduction in hemoglobin A1C from 8.6 to 6.5 percent with no changes in insulin dose, dietary intake, or body weight [18].

Heart failure

ARBs and ACE-I are also efficacious in secondary prevention of morbidity and mortality in patients with existing heart failure, especially with concomitant coronary artery disease, due to

10. Review of Harms and Toxicity and Summary of Evidence on Safety

The safety of ARBs has been evaluated in a variety of contexts, both relative to placebo and relative to ACE-i, as follows:

a. Reduction in glomerular filtration rate (GFR)
b. Hyperkalemia
c. Cough
d. Angioedema
e. Teratogenicity

11. Summary of Available Data on Comparative Cost and Cost-effectiveness

Costs

According to the Management Sciences of Health International Drug Price Indicator Guide 2014, Losartan 50mg has a median buyer price of $0.0202/tab. Costs range from $0.0097/tab for the Ministry of Health of Peru to $0.0764 for the Sudan National Health Insurance Fund. Irbesartan, the other ARB listed, is priced at $0.24/tab in the Dominican Republic.

Cost Effectiveness of ARB’s for Hypertension

The majority of cost effectiveness analyses of ARB’s have been conducted prior to the availability of generic losartan by the FDA in April 2010. Despite this limitation, ARB’s have been demonstrated to be cost effective in several contexts when compared to other classes of anti-hypertensives.

A cost effectiveness analysis of the LIFE study comparing losartan to atenolol for hypertensive patients with left ventricular hypertrophy in the UK, found that the incremental cost-effectiveness ratio (ICER) for was $3973.09 for each quality adjusted life year (QALY) for the losartan treatment group, which was determined to be cost effective in the UK context [32]
An observational retrospective cohort analysis from 2010 and 2011 of 28,165 beneficiaries of a private medical insurance company in South Africa comparing hypertensive patients treated with either an ACEi or an ARB demonstrated a statistically significant higher cost for ARB therapy. The annual downstream cost per patient of ARB therapy was estimated at $601.50 verses $452.61 for ACEi therapy, at 24.7% higher cost for ARB therapy. However, this analysis was limited by grouping all ACEi and ARB drugs and was completed when the unit price of losartan in South Africa was $0.0744 in 2010 compared to the most recent 2014 price of $0.0202. [33]

Cost Effectiveness in Diabetic Patients

Given ARB’s proven ability prevent progression of diabetic nephropathy, a cost effectiveness analysis comparing the treatment of hypertension in type 2 diabetic patients with overt nephropathy found that Irbesartan was cost saving compared to Amlodipine in the UK setting. The analysis concluded that a 10 year cost savings of $6371.91 with the majority of cost saved with the delay of treatment of end stage renal disease. [34]

A cost effectiveness analysis conducted on a meta-analysis of ACEi vs ARBs in patients with diabetic nephropathy to prevent ESRD found ARB’s to be more cost effective. The cost to prevent one patient from developing ESRD was $31,729 for ARBs and $51,585 for ACEi in the US third-party payer context. [35]

Cost Effectiveness in Heart Failure

A cost effectiveness analysis of the ELITE study comparing losartan to captopril for patients with symptomatic heart failure and a left ventricular ejection fraction less than 40 percent, demonstrated losartan to be more cost effective than captopril. It was estimated that the lifetime cost of losartan treatment was $54 less than captopril treatment. However, as there were no observed differences in clinical outcomes between the two medications, the cost effectiveness was predicated on the lower cost of losartan compared to captopril in the US market. [36]

Cost Effectiveness of Specific ARB’s

There are several cost-effectiveness comparisons between ARB’s in the literature that draw differing conclusions on the most cost effective ARB choice.

A cost effectiveness study of ARB monotherapy in adult patients with hypertension in the Netherlands found olmesartan to be the most cost effective ARB. When compared to losartan, valsartan and irbesartan, olmesartan was found to be the most cost effective for cost per cardiovascular event averted. Costs for one cardiovascular event averted for olmesartan was calculated to be $43,738. [37]
A comparison of cost effectiveness of candesartan versus generic losartan in the management of hypertension and heart failure in the UK NHS setting estimated a cost per quality adjusted life year gained by using candesartan instead of losartan to exceed $49,000. Given this, generic losartan was demonstrated to be the cost effective ARB and the use of losartan over candesartan was estimated to save the UK NHS approximately $250 million per year in drug costs. (38)

12. Summary of Regulatory Status of the Medicine

United States Food and Drug Administration (FDA)- Approved April 14, 1995 – Generic approved April 7 2010
Indications:
- Treatment of hypertension, to lower blood pressure in adults and children greater than 6 years old. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy. There is evidence that this benefit does not apply to Black patients.
- Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension.

European Medicines Agency (EMA)- Approved
Indications:
- Treatment of essential hypertension.
- Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilized with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilized under the treatment of the chronic heart failure.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

Australian Therapeutic Goods Administration-Approved
- Hypertension COZAAR is indicated for the treatment of hypertension. It may be
used alone or in combination with other antihypertensive agents (eg. thiazide diuretics).

- Renal Protection in Type 2 Diabetic Patients with Proteinuria COZAAR is indicated to delay the progression of renal disease in hypertensive type 2 diabetics with proteinuria, defined as urinary albumin to creatinine ratio ≥300mg/g.

Japan Pharmaceuticals and Medical Devices Agency – Approved
(English text not available)

Canada- Approved

- Hypertension: ACT LOSARTAN (losartan potassium) is indicated for the treatment of essential hypertension. ACT LOSARTAN is also indicated in patients with essential hypertension and left ventricular hypertrophy.
- ACT LOSARTAN may be used alone or concomitantly with thiazide diuretics.
- A great majority of patients with severe hypertension in controlled clinical trials required combination therapy. Losartan potassium has been used concomitantly with beta-blockers and calcium channel blockers, but the data on such use are limited.
- Type 2 Diabetic Patients with Proteinuria and Hypertension: ACT LOSARTAN is also indicated to delay the progression of renal disease as measured by the occurrence of doubling of serum creatinine, and end stage renal disease, and to reduce proteinuria.

13. Availability of Pharmacopoeial Standards


14. Reference List


