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 WITH REDUCED EJECTION FRACTION, AND CHRONIC KIDNEY DISEASE

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1. Executive Summary

Hypertension is the leading risk factor for death worldwide [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 (WHO) 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, intolerance of ACE-I, due principally to cough but also angioedema and other toxicities, is common. High-quality data suggests cough occurs in 4-20% of ACE-I users [4,5,6], and angioedema in 0.3% to 0.7% [6,7]. Moreover, the incidence of these adverse events may be significantly higher in certain subpopulations in low- and middle-income countries. A case-control study in people of Chinese ancestry reported persistent cough in 44% of ACE-I users [7], and sub-studies in persons of African ancestry report rates of angioedema of 2.8 to 4.5 times greater than the general population [6,8,9,10]. A substantial minority of persons who would benefit from ACE-I therapy therefore fail to do so because of intolerance to potentially life-threatening adverse effects.

Angiotensin-receptor blockers (ARBs) act on a near-identical biological pathway as ACE-I, inhibiting the renin-angiotensin system by blocking renal receptors for angiotensin instead of preventing its generation in the lung. However, their risk of the adverse effective above is significantly lower. High-quality evidence from randomized controlled trials and meta-analyses demonstrates that the incidence of cough is approximately 68% less with ARBs than ACE-I [11], and the incidence of angioedema is approximately 67% lower [6,8,12], with comparable risk of hyperkalemia [6]. Moreover, systematic reviews of direct comparisons of ARBs with ACE-I suggest that their clinical efficacy is comparable in most populations [11,13,14,15]; the price of ACE-I and ARBs in developing countries is comparable [16]; and their cost-effectiveness for the conditions above is equivalent [17,18,19].

ARBs are therefore routinely employed worldwide for the same conditions as ACE-I, especially for persons unable to tolerate ACE-I due to adverse effects such as cough and angioedema. However, unlike ACE-I, 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, chronic heart failure with reduced ejection fraction, or chronic kidney disease who cannot tolerate ACE-I.
2. **Name of the focal point in WHO submitting or supporting the application**

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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-box representative of therapeutic group (angiotensin receptor blockers)

7. **Treatment Details**

Because ACE-I and ARBs act by a similar biological mechanism, ARBs are indicated as an alternative to ACE-I for intolerant patients according to multiple guidelines, and as an equivalent substitute for ACE-I naïve patients in others. Like ACE-I, ARBs lower blood pressure by modulating the renin-angiotensin-aldosterone system. Whereas ACE-I prevent the pulmonary conversion of angiotensin I to angiotensin II, ARBs prevent angiotensin II, once generated, from binding to angiotensin II AT1 receptors in the kidney. The similar net result is impaired secretion of vasopressin and impaired production and generation of aldosterone, with an associated decrease in blood pressure, decreased myocardial oxygen demand, and decreased intra-glomerular pressure.

The 2014 Evidence-Based Guidelines for the Management of High Blood Pressure in Adults, authored by the Eighth Joint (US) National Committee (JNC-8) recommend the use of ARBs or ACE-I as possible first-line agents for essential hypertension, alone or in combination for all non-black populations, and as definite first-line agents for essential
hypertension for persons with CKD, regardless of race [20]. The 2013 European Society of Cardiology Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases recommend ACE-I or ARBs for persons with diabetes and hypertension, especially with concomitant coronary artery disease [21], to reduce morbidity and mortality.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of Heart Failure and the 2016 European Society of Cardiology (ESC) Guidelines for the Treatment of Acute and Chronic Heart Failure recommend the use of ARBs for reduction of morbidity and mortality in patients with heart failure and reduced ejection fraction who are ACE-I intolerant [22,23]. The ACC/AHA guideline also recommends ARBs as a reasonable alternative to ACE-I for treatment-naïve persons already taking ARBs [22].

ARBs, like ACE-I, are also indicated in persons with CKD for renal protection, independent of blood pressure value. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines for evaluation and management of CKD [24] recommends either an ARB or ACE-I for all persons with CKD with urine albumin excretion of more than 300 mg per day, to prevent and control proteinuria and consequent nephropathy.

For all indications, 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 1. Starting and target doses of commonly used ARBs.

<table>
<thead>
<tr>
<th>Angiotensin Receptor Blocker (ARB)</th>
<th>Starting Dose (mg)</th>
<th>Target Dose (mg)</th>
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<tbody>
<tr>
<td>Candesartan</td>
<td>4-8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150 mg daily</td>
<td>300 mg daily</td>
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<tr>
<td><strong>Losartan</strong></td>
<td><strong>25 mg daily</strong></td>
<td><strong>100 mg daily</strong></td>
</tr>
<tr>
<td>Olmesartan</td>
<td>20 mg daily</td>
<td>40 mg daily</td>
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<tr>
<td>Telmisartan</td>
<td>40 mg daily</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>50 mg daily</td>
<td>150 mg daily</td>
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</table>

8. Information Supporting Public Health Relevance

The burden of hypertension is rapidly increasing, especially in low- and middle-income countries. Hypertension caused 9.4 million deaths in 2012 and 10.4 million in 2013, and caused the loss of 7% of all disability-adjusted life years (DALYs) worldwide in 2010 [25,26]. Between 1975 and 2015, hypertension rates nearly doubled worldwide, with the highest prevalence now in low-income countries [27]. Hypertension contributes to coronary heart disease, myocardial infarction, stroke, chronic kidney disease, and heart failure, among other conditions [28,29]. The INTERHEART study demonstrated that
Hypertension increases the odds of myocardial infarction by 1.91 [95% CI 1.74-2.10] with a population attributable risk of 17.9% [95% CI 15.7-20.4%], after adjustment for gender, age, and region of the world [30]. Hypertension is a major risk factor for heart failure, and the predominant cause of heart failure in Africa and the Americas [31,32]. It is also the predominant etiology of chronic kidney disease, the prevalence of which rose 32% worldwide from 2005 to 2015 [33]. The number of people in Africa alone with hypertension is expected to increase 68% from 75 million in 2008 to approximately 125 million in 2025. [32].

There is high quality evidence that hypertension control is both effective and cost-effective in reducing the risk of these conditions. A reduction in systolic blood pressure of 5 mmHg would reduce all-cause mortality by 7% and stroke by 14% [34]. Fully optimal blood pressure control worldwide could save $370 billion dollars annually [35]. However, rates of blood pressure awareness and treatment remain poor, especially in developing countries. The Prospective Urban Rural Epidemiology (PURE) study, which examined 154,000 adults in 17 countries, found that only 47% of subjects with hypertension were aware of their diagnosis, and while 88% of those were receiving medical treatment, only 33% achieved blood pressure control [36]. However, in low-income countries only 41% of persons with hypertension were aware, 32% were treated, and 13% controlled [36].

Disparities in the incidence and control of heart failure and CKD also persist across country settings, and these are driven largely by gaps in control of hypertension. A 2013 systematic review of worldwide risk factors for heart failure (with both reduced and preserved ejection fraction) found that fewer than 10% of heart failure cases in Africa, for example, were associated with ischemic heart disease, whereas 33% were associated with hypertension [37]; isolated studies have found hypertension in 60-80% of Africans with heart failure [38,39,40,41]. Similarly, a 2015 systematic review of the burden of chronic kidney disease worldwide found prevalence of 9% and 10% in men and women in developed countries, but 11% and 12% in men and women in developing countries – such that 78% of all persons with CKD worldwide now reside in developing countries [42].

Gaps in access to and use of antihypertensive and other cardiovascular medications drive these disparities in treatment and control of hypertension, heart failure, and CKD across countries, and consequent disparities in CVD outcomes. For example, secondary analyses of the PURE data examining access to aspirin, beta blockers, ACE-I, and statins, showed that the availability and affordability of these medications decreased from low- to high-income countries [43]. In addition, in low- and middle-income countries, patients with previous CVD were less likely to use any of these four medications if fewer than four were available [43]. Prevalence of ACE-I and ARB use among eligible populations was as low as 5% in low-income countries [44]; large disparities in country-level use suggest medication availability and cost (as opposed to individual-level variables) as the primary causes of these low adherence rates [44]. The use of ARBs for control of hypertension, heart failure with reduced ejection fraction, and CKD in patients for whom ACE-I are unavailable, prohibitively expensive, or poorly
tolerated could substantially control the growing impact of these diseases on cardiovascular and overall mortality.

9. Review of Benefits and Summary of Comparative Effectiveness

Considerable high-quality data has demonstrated the efficacy of ACE-I for the treatment of hypertension as well as primary and secondary prevention of CVD in individuals with diabetes mellitus, heart failure with reduced ejection fraction, and myocardial infarction among other conditions [6,8,12]. This impact occurs through multiple pathways, such as reduced sympathetic activity, inhibited release of endothelin, and cytokine modulation associated with inhibition of the renin-angiotensin system [13,14,15]. These medications are low cost, widely available in high-income countries [16], and are generally well-tolerated, such that their inclusion on the WHO EML was approved in 2002 [3].

However, ACE-I frequently cause cough secondary to increased bradykinin because of ACE-I-mediated inhibition of pulmonary kininase activity [4,5,7]. Also a result of this enzyme inhibition, ACE-I can cause angioedema in 0.1% to 0.8% of individuals, with an increased rate of up to fivefold in people of African descent [6,8,9,10]. A randomized, double-blind, controlled trial of 12,557 people with hypertension treated with enalapril found a significantly increased risk of angioedema among those defined as black race (OR 2.88, 95% CI 1.72-4.82) [8]. This is supported by several other publications, including a retrospective cohort study showing an adjusted relative risk of angioedema among black American users to be 4.5 (95% CI 2.9-6.8) when compared to white American users [9]. The data on ACE-I use in sub-Saharan Africa are limited, though there are case reports detailing serious near-fatal or fatal complications. Despite this frequency of adverse effects, there is currently no ACE-I alternative on the EML, particularly for the indications of heart failure with reduced ejection fraction and the management of hypertension in patients with diabetes mellitus with nephropathy. While ACE-I would remain the first-line recommendation, it is important to include ARBs as a potential substitute to ACE-I therapy among those who do not tolerate ACE-I.

As compared to ACE-I, ARBs are associated with markedly lower incidence of cough because they inhibit the renin-angiotensin system by blocking angiotensin II from binding to the AT1 receptor [9]. Additionally, a high quality study, ONTARGET, showed decreased rates of angioedema with the ARB telmisartan compared with ACE-I ramipril, while also demonstrating non-inferiority for preventing clinical outcomes [6]. Overall, ARBs have been shown to achieve the same cardiovascular event reductions as well as blood pressure reductions as ACE-I, but are more tolerable given reduced adverse events, particularly cough. Several direct randomized comparisons have shown no difference in efficacy between ARBs and ACE-I, while showing reduced adverse effects [13,14,15]. Other indirect comparisons, including trials in which ARBs and ACE-I, respectively, were compared to placebo, showed no difference between classes. ARBs remain as effective as ACE inhibitors for the indications above, as follows:

Hypertension
The efficacy of ACE-I in blood pressure control, and consequent prevention of cardiovascular morbidity and mortality, is well-established, and high-quality evidence demonstrates that ARBs provide equivalent effect. A 2006 systematic review by Matchar et al [6] found no significant difference in blood pressure lowering between ACE-I and ARBs across 61 studies involving more than 15,000 patients [9]. A 2014 Cochrane systematic review by Li et al [13], who examined nine studies with 11,007 participants, found no significant difference between ACE-I and ARB with respect to total mortality; total cardiovascular events; or cardiovascular mortality among patients with hypertension. A 2016 systematic review of randomized trials by Bangalore et al in more than 250,000 patients without heart failure [14] 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 [14].

Heart failure with reduced ejection fraction

ACE-I and ARBs are also efficacious in secondary prevention of morbidity and mortality in patients with existing heart failure with reduced ejection fraction, especially with concomitant coronary artery disease, likely due to their inhibition of intra-cardiac renin-angiotensin pathways that cause myocardial hypertrophy and remodeling [45]. A meta-analysis of five trials, involving 12,763 patients with heart failure with reduced ejection fraction found [46] that use of an ACE-I substantially decreased risk of all-cause death, readmission for heart failure, and myocardial infarction. A randomized trial of valsartan in chronic heart failure found, similarly, a significant decrease in mortality and morbidity; signs and symptoms of heart failure; and hospitalizations for treatment relative to placebo [47]. Another high quality trial by the VALIANT Investigators showed non-inferiority of valsartan compared to captopril among patients with post-myocardial infarction with reduced ejection fraction [48]. Based on these data and others, 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-I intolerant [22,23].

Chronic Kidney Disease

ACE-I and ARBs may be superior to other anti-hypertensives in the secondary prevention of cardiovascular events in persons with (CKD) [21] because, in addition to their impact on blood pressure control, these medications influence other renal sequelae, such as proteinuria. A meta-analysis of the effect of monotherapy and combination therapy with ACE-I and ARBs for CKD in 6181 participants [48] found that both significantly reduced proteinuria relative to both placebo and calcium channel blockers (RR 0.66, 95% CI 0.63-0.69 and 0.62, 95% CI 0.55-0.7, respectively) over 5 to 12 months and that both were equally effective. The European Society of Cardiology and European Association for the Study of Diabetes guidelines on diabetes, pre-
diabetes, and cardiovascular disease therefore strongly recommend ACE-I and ARB for secondary prevention of CVD in persons with these conditions [21].

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. In the ONTARGET trial comparing telmisartan with ramipril, telmisartan was associated with a greater mean decrease in blood pressure, but a significantly higher rate of hypotensive symptoms [6]. However, there was a lower rate of cough (1.1% versus 4.2%) and angioedema (0.1% versus 0.3%) with telmisartan compared to ramipril, respectively [6]. The TRANSCEND investigators examined 5926 patients deemed intolerant to ACE-I and showed very low rates of both cough (0.5%) and angioedema (0.07%), with both having no statistically significant difference in incidence in these side effects when compared to the placebo group [12]. Conversely, one study found the rate of angioedema among 12,577 patients receiving enalapril to be 0.68% [8], and others report up to 20% of patients receiving ACE-I experience cough [22]. A moderate-quality multicenter randomized trial of 100 patients showed a much higher rate of cough among patients receiving lisinopril than losartan (88% vs 37%, respectively, p ≤ 0.001) [49]. The rate of hyperkalemia was comparable in both groups in the ONTARGET trial (3% and 3% for ramipril and telmisartan, respectively).

Both drug types are contraindicated in pregnancy – ARBs due in part to feedback disinhibition of renin release that could activate the fetal AT2 receptor [50]. Lastly, there is evidence that olmesartan may rarely produce a sprue-like enteropathy, which resolves on cessation of the drug. A French cohort trial of some 4.5 million patients on olmesartan established a number-needed-to-harm (NNH) of 12,550 for olmesartan treatment to cause one case of severe enteropathy [51], and no increased risk in users of other ARBs.

ARBs are therefore, on balance, as safe as ACE-I when used according to established indications and doses. This result has also been confirmed in recent work comparing the incidence of withdrawals due to all adverse effects (WDAE) between the two drug categories. A 2014 Cochrane systematic review found high quality evidence supporting a lower incidence of WDAE for ARBs relative to ACE-I (relative risk 0.83, 95% CI 0.74-0.93), due in large part to a difference in incidence of cough [13]. A 2016 meta-analysis involving more than 250,000 patients from randomized trials found a larger gap [14]: the relative risk of WDAE in ARBs relative to ACE-I was 0.72 (95% CI 0.85-0.81), suggesting that ARBs are more tolerable than ACE-I. In addition, several studies have compared the tolerability of ARBs with other medications, including thiazide diuretics and amlodipine, and have not shown significant side effects of combination therapies [52,53]. In particular, an October 2016 meta-analysis examining the relative discontinuation rates of antihypertensive drug classes found that among all classes of drugs studied (diuretics, beta-blockers, calcium channel blockers, ACE-I, ARBs, and centrally-acting agents), ARBs were the only drug class that did not significantly increase discontinuation from adverse events relative to placebo [53].
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, generic 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.

In comparison, the median buyer price of generic enalapril 5mg is $0.0165/tab with a range of $0.0083/tab from Mission for Essential Drugs and Supplies in Kenya to $0.0283/tab from Action Medeor International Healthcare in Tanzania.

Cost Effectiveness of ARBs for Hypertension

The majority of cost effectiveness analyses of ARBs have been conducted prior to the approval of generic ARBs by the FDA and other regulators. Even in the pre-generic era, evidence suggests that ARBs are cost-effective relative to other classes of antihypertensives for multiple indications [17,18,19,54,55], and the cost of losartan has dropped significantly as generics have become available on the market [56]. In 2009, the median buyer price of losartan 50mg was listed at $0.3182/tab. In 2010, the year that generic losartan was approved, the price dropped 85% to 0.0483/tab. Losartan has therefore followed the typical pattern of evolution of pricing for antihypertensives, with an 80-90% price reduction in the year after genericisation and a gradual decrease thereafter.

A 2006 cost effectiveness analysis of the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study comparing losartan to atenolol for hypertensive patients with left ventricular hypertrophy in the UK, found that the incremental cost-effectiveness ratio (ICER) was $3,973 for each quality adjusted life year (QALY) for the losartan treatment group, which was determined to be cost effective in the UK context [54].

In South Africa, an observational retrospective cohort analysis of 28,165 hypertensive individuals from 2010-2011 demonstrated a statistically significant higher cost for ARB therapy than ACE-I, with total annual downstream cost per patient estimated at $452.61 for ACE-I therapy and $601.50 for ARB therapy (32.9% greater) [17]. However, this analysis was limited by its grouping of all ACE-I and ARB drugs together; and was conducted when the unit price of losartan was 7.4 cents in South Africa, compared to 2.0 cents in 2014 [17]. In both these contexts and others, the increasing availability and decreasing cost of generic ARBs makes the case for their cost-effectiveness for hypertension control and other indications more compelling than prior data suggests.

Cost Effectiveness for Heart Failure with Reduced Ejection Fraction
A 1999 cost effectiveness analysis of the Evaluation of Losartan in the Elderly Study (ELITE) study, which compared losartan to captopril for patients with symptomatic heart failure and a left ventricular ejection fraction less than 40% in patients age >65 years old, demonstrated that losartan was cost effective. It was estimated that the lifetime cost of losartan treatment was $54 less than captopril treatment. Like the analyses above, this study was conducted in the pre-ARB generic era, when branded losartan was estimated to cost over three times the cost of generic captopril [19].

Cost Effectiveness for Chronic Kidney Disease

Given ARBs' efficacy in preventing diabetic nephropathy, cost-effectiveness data also exists for their prevention of end-stage renal disease and other sequelae of CKD, even when ARBs were priced far higher than today. A 2004 cost effectiveness analysis of the use of irbesartan in treating hypertension, type II diabetes, and nephropathy in the UK found net cost-savings relative to both control and amlodipine, due chiefly to prevention and delayed onset of end-stage renal disease [55]. The analysis concluded that treatment with an ARB instead of a calcium channel blocker resulted in a 10-year cost savings of $6372. Given that losartan cost $1418 per year in the UK in 2003 and approximately $19 per year in 2016, it is likely that generic ARBs are considerably more cost-effective at present than these data suggest.

A cost effectiveness study conducted on a meta-analysis comparing ACE-I vs ARBs found ARBs to be more cost-effective in preventing patients with diabetic nephropathy from progressing to ESRD in the Greek context as well. The cost to prevent one patient from developing ESRD was $31,729 for ARBs and $51,585 for ACE-I. The study demonstrated ARBs to be an overall net cost saving to the health care system estimated at $7770 per patient over three years. This study, too, utilized 2006 prices- in which ARBs in the Greek system cost nearly five times as much as ACE-I ($763.50 vs $144.92) [18].

Cost Effectiveness of Losartan as the Exemplar for ARBs

To our knowledge, there have been no cost effectiveness analyses of head-to-head trials of ARBs to enable direct conclusions about the most cost-effective ARB. Several studies and real world examples suggest that losartan may be the most cost-effective ARB in varying contexts.

A comparison of cost effectiveness of candesartan vs. losartan in the management of hypertension and heart failure in the 2011 UK NHS setting estimated a cost per QALY gained by using candesartan instead of losartan to exceed $49,000. Given this, generic losartan was demonstrated to be the cost-effective ARB in the UK context. The preferential use of losartan over candesartan was estimated to save the UK NHS approximately $250 million per year in drug costs [57].

In 2011 based on a cost saving strategy, the Danish health care system delisted all ARBs except for losartan. This endeavor increased the percentage of losartan...
prescriptions out of all ARB prescriptions from 31% to 93%. This is estimated to have saved the Danish system a $41 million USD per year [58].

12. Summary of Regulatory Status of the Medicine


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 mellitus 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

Indications:
- Hypertension COZAAR (losartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents (e.g., thiazide diuretics).
- Renal protection in type 2 diabetes mellitus with proteinuria COZAAR (losartan) 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)
Indications:
- 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 diabetes mellitus with proteinuria and hypertension: 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. References


diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2013 Oct 14;34(39):3035-87.


54. McInnes G, Burke T a, Carides G. Cost-effectiveness of losartan-based therapy in patients with hypertension and left ventricular hypertrophy: a UK-based