COMMENTS FROM THE DEPARTMENT OF NONCOMMUNICABLE DISEASES, REHABILITATION AND DISABILITY ON THE PROPOSAL FOR ADDITION OF TRIPLE DRUG FIXED DOSE ANTIHYPERTENSIVE MEDICINE COMBINATIONS ON THE MODEL LIST OF ESSENTIAL MEDICINES FOR TREATMENT OF ESSENTIAL HYPERTENSION IN ADULTS

The application was submitted by The George Institute for Global Health and was not developed in collaboration with the WHO Department of Noncommunicable Diseases, Rehabilitation and Disability, although a brief consultation with the department took place prior to submission.

The technical unit supports the application to add triple drug fixed-dose anti-hypertensive medicine combinations to the 24th WHO Model List of Essential Medicines, but with certain conditions:

Step up/Replacement therapy for hypertension:

- The triple drug antihypertensive fixed-dose combinations (FDCs) are recommended as "step-up" therapy for patients who do not achieve adequate blood pressure control with dual therapy (1-2).
- The triple drug FDCs can also be used as a "replacement" strategy for patients already taking three separate antihypertensive medicines, to improve treatment adherence and simplify regimens (3-4).
- Triple-combination therapy is efficacious for moderate to severe hypertension, with substantial additional BP reduction over dual regimens and well tolerated with adverse event profiles similar to dual regimens (5).

Initial/early treatment of hypertension with low-dose combinations:

- As per new emerging evidence, the low dose triple combinations antihypertensive drugs can be considered as an alternative for monotherapy because of better blood pressure reduction with fewer adverse effects (7-11).
- Assess the implications of introducing the triple FDC on national procurement systems, including potential benefits from reduced logistics and inventory complexity versus the upfront costs of transitioning to a new medication. Consideration must be given to negotiating bulk purchasing agreements, ensuring generic availability, and integrating the FDC into existing essential medicines lists to optimize affordability and sustainability within constrained health budgets

The combinations for consideration are:

- Amlodipine + Valsartan + Hydrochlorothiazide, 5 mg + 160 mg + 12.5 mg
- Amlodipine + Valsartan + Hydrochlorothiazide, 5 mg + 160 mg + 25 mg
- Amlodipine + Valsartan + Hydrochlorothiazide, 10 mg + 160 mg + 12.5 mg
- Amlodipine + Valsartan + Hydrochlorothiazide, 10 mg + 160 mg + 25 mg
- Amlodipine + Valsartan + Hydrochlorothiazide, 10 mg + 320 mg + 12.5 mg

- Amlodipine + Olmesartan + Hydrochlorothiazide, 5 mg + 20 mg + 12.5 mg
- Amlodipine + Olmesartan + Hydrochlorothiazide, 5 mg + 40 mg + 12.5 mg
- Amlodipine + Olmesartan + Hydrochlorothiazide, 5 mg + 40 mg + 25 mg
- Amlodipine + Olmesartan + Hydrochlorothiazide, 10 mg + 40 mg + 12.5 mg
- Amlodipine + Olmesartan + Hydrochlorothiazide, 5 mg + 20 mg + 25 mg

- Amlodipine + Telmisartan + Indapamide, 1.25 mg + 10 mg + 0.625 mg
- Amlodipine + Telmisartan + Indapamide, 2.5 mg + 20 mg + 1.25 mg
- Amlodipine + Telmisartan + Indapamide, 5 mg + 40 mg + 2.5 mg

- Amlodipine + Perindopril + Indapamide, 5 mg + 5 mg + 1.25 mg
- Amlodipine + Perindopril + Indapamide, 10 mg + 5 mg + 1.25 mg
- Amlodipine + Perindopril + Indapamide, 5 mg + 10 mg + 2.5 mg
- Amlodipine + Perindopril + Indapamide, 10 mg + 10 mg + 2.5 mg

Note: Majority of these individual drugs are already part of WHO HEARTS protocol (12).

Target Population of the application includes:

Main Indication

- For treatment of hypertension in patients with uncontrolled BP despite receiving dual antihypertensive drug therapy
- For treatment of hypertension in patients currently prescribed three antihypertensive medicines provided as separate pills, to reduce pill burden

Secondary indication (for low-dose triple drug FDCs)

- For treatment of hypertension in patients uncontrolled on antihypertensive drug monotherapy or for initial treatment in those with high absolute CVD risk and/or >20/10mmHg from target BP.

Current WHO Recommendations

The World Health Organization (WHO) Guideline for the Pharmacological Treatment of Hypertension in Adults (2021) recommends a stepwise approach to antihypertensive therapy, incorporating up to three drug classes as needed to achieve blood pressure control. The use of fixed-dose combinations (FDCs) is encouraged when available, to improve adherence and simplify treatment regimens. The guideline identifies three primary classes of antihypertensive medications as preferred options, both individually and in combination:

1. Angiotensin-Converting Enzyme Inhibitors (ACEi) or Angiotensin II Receptor Blockers (ARB)
2. Long acting dihydropyridine Calcium Channel Blockers (CCB)
3. Thiazide or thiazide-like diuretics

These classes form the foundation of recommended treatment protocols in the WHO guideline and are also consistently endorsed by other international hypertension management frameworks (12).

Effectiveness

- Evidence shows that FDCs lead to more rapid achievement of target blood pressure levels and better long-term control compared to monotherapies or stepwise titration of individual drugs
- From a patient compliance perspective, FDCs reduce pill burden, simplify dosing regimens, and improve treatment adherence, while from health system side it helps in simplified logistic and supply chain. Low-dose triple combination therapy confers larger BP reduction and has lower risk of side effects than with full dose monotherapy

Adverse Effects

- No significant difference in the incidence or severity of adverse events when compared to separate monotherapies
- Dose titration is limited (individual dose components cannot be adjusted)

Affordability

- In many LMICs, triple FDCs remain less affordable than equivalent three-pill regimens due to limited local production and manufacturing capacity (13)
- While current market prices for FDCs may be higher, their inclusion in the EML could catalyze more favorable pricing through bulk procurement, generic entry, and increased international financing mechanisms.

Regulatory Consideration

- Regulatory landscape pathways for approving FDCs may need to be reviewed, particularly when all component drugs are already individually registered

Other Clinical Considerations

- In patients with several renal impairment these FDCs are not recommended, while for mild to moderate renal impairment lab monitoring is required (12).
- Before initiating and several weeks after starting triple combination therapy consider checking serum creatinine and potassium (12).

Conclusion

Fixed dose combination (FDC) for anti-hypertensives is not widely available in countries, especially LMICs, mainly due to higher costs compared with an equivalent three-pill regimen (13). While the efficacy, safety, and potential societal cost savings of FDCs have been well established, this is not the same case for countries that depend heavily on importing anti-hypertensive medicines. Furthermore, while FDCs offer clear advantages in improving treatment adherence (5), efforts to advocate for their inclusion in the WHO Essential Medicines List must critically address issues of affordability and supply sustainability. Given that the WHO Essential Medicines List serves as a key reference for national procurement and reimbursement policies, the inclusion of FDCs could catalyze wider adoption, stimulate competitive market dynamics to lower prices, and significantly enhance access within health systems facing resource constraints.

References

1. *Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127-e248.*
2. *McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension: Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO). European Heart Journal. 2024:ehae178.*
3. *Satheesh G, Dhurjati R, Huffman MD, Rosende A, Rodgers A, Prabhakaran D, et al. Standardized treatment protocols for hypertension: global availability, characteristics, and alignment with the hypertension guideline recommendations. Journal of Hypertension. 2024;42(5):902-8.*
4. *Düsing R, Waeber B, Destro M, Santos Maia C, Brunel P. Triple-combination therapy in the treatment of hypertension: a review of the evidence. J Hum Hypertens. 2017 Aug;31(8):501–10.*
5. *Sung J, Ahn KT, Cho B, Lee SY, Kim BJ, Kim DK, et al. Adherence to triple-component antihypertensive regimens is higher with single-pill than equivalent two-pill regimens: A randomized controlled trial. Clinical Translational Sci. 2021 May;14(3):1185–92.*

6. *Huffman MD, Baldridge AS, Lazar D, Abbas H, Mejia J, Flowers FM, et al. Efficacy and safety of a four-drug, quarter-dose treatment for hypertension: the QUARTET USA randomized trial. Hypertens Res. 2024 Jun;47(6):1668–77.*
7. *Wang N, Rueter P, Atkins E, Webster R, Huffman M, De Silva A, et al. Efficacy and Safety of Low-Dose Triple and Quadruple Combination Pills vs Monotherapy, Usual Care, or Placebo for the Initial Management of Hypertension: A Systematic Review and Meta-analysis. JAMA Cardiol. 2023 Jun 1;8(6):606.*
8. *Bennett A, Chow CK, Chou M, Dehbi HM, Webster R, Salam A, et al. Efficacy and Safety of Quarter-Dose Blood Pressure–Lowering Agents: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Hypertension. 2017 Jul;70(1):85–93.*
9. *Webster R, Salam A, De Silva HA, Selak V, Stepien S, Rajapakse S, et al. Fixed Low-Dose Triple Combination Antihypertensive Medication vs Usual Care for Blood Pressure Control in Patients With Mild to Moderate Hypertension in Sri Lanka: A Randomized Clinical Trial. JAMA. 2018 Aug 14;320(6):566.*
10. *Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP, et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. The Lancet. 2021 Sep;398(10305):1043–52.*
11. *Ojji DB, Salam A, Sani MU, Ogah OS, Schutte AE, Huffman MD, et al. Low-Dose Triple-Pill vs Standard-Care Protocols for Hypertension Treatment in Nigeria: A Randomized Clinical Trial. JAMA. 2024 Oct 1;332(13):1070.*
12. *HEARTS Technical package for cardiovascular disease management in primary health care: evidence-based treatment protocols. Geneva: World Health Organization; 2018 (WHO/NMH/NVI/18.2). Licence: CC BY-NC-SA 3.0 IGO. World Health Organization;*
13. *O'Hagan E, McIntyre D, Nguyen T, Tan KM, Hanlon P, Siddiqui M, et al. A Cross-Sectional Survey of Fixed-Dose Combination Antihypertensive Medicine Prescribing in Twenty-Four Countries, Including Qualitative Insights. gh. 2024 Sep 12;19(1):73.*