Valsartan + amlodipine + hydrochlorothiazide
Statut de médicament essentiel
Section:
12. Cardiovascular medicines 12.3. Antihypertensive medicines
Codes ATC: C09DX01
Indication
Essential hypertension Code ICD11: BA00.Z
INN
Valsartan + amlodipine + hydrochlorothiazide
Type de médicament
Chemical agent
Type de liste
Liste de base
Formulations
Oral > Solid > dosage form: 160 mg + 5 mg + 12.5 mg ; 160 mg + 5 mg + 25 mg ; 160 mg + 10 mg + 12.5 mg ; 160 mg + 10 mg + 25 mg ; 320 mg + 10 mg + 25 mg
Historique des statuts LME
Ajouté pour la première fois en 2025 (TRS 1064)
Sexe
Tous
Âge
Adolescents et adultes
Équivalence thérapeutique
Des médicaments appartenant à la même classe pharmacologique peuvent être utilisés
Limites de l'équivalence thérapeutique
Therapeutic alternatives are medicines in the 4th level ATC chemical subgroup C09CA Angiotensin II receptor blockers (ARBs), plain (for valsartan); C08CA Dihydropyridine derivatives) (for amlodipine); and chlorthalidone, chlorothiazide and indapamide (for hydrochlorothiazide)
Renseignements sur le brevet
Patents have expired in most jurisdictions
Lire la suite sur les brevets.
Wikipédia
Valsartan + amlodipine + hydrochlorothiazide
DrugBank
Valsartan ,
Amlodipine ,
Hydrochlorothiazide
Recommandation du comité d'experts
☐
The Expert Committee acknowledged the substantial global burden of hypertension and its role as a major risk factor for cardiovascular disease. The Committee also acknowledged the role of combination therapy, using either multiple single agent antihypertensives or fixed-dose combinations, in the management of hypertension, as recommended in WHO guidelines. The Committee noted the benefits of triple combination antihypertensive therapy for reductions in systolic and diastolic blood pressure and some evidence of improved adherence and persistence compared with free equivalent combination therapy. Adverse effects are generally mild and manageable, and consistent with the known adverse event profiles of the components. Based on these considerations, the Expert Committee recommended the inclusion of triple fixed-dose combination antihypertensive formulations containing a long-acting dihydropyridine calcium channel blocker, an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, and a thiazide or thiazide-like diuretic on the core list of the EML based on a favourable balance of benefits to harms. Listing is recommended for valsartan + amlodipine + hydrochlorothiazide and perindopril + amlodipine + indapamide, with each component with a square box, indicating that other medicines within the respective pharmacological classes represent therapeutic alternatives for national selection. The Committee emphasized that triple fixed-dose combinations are intended to complement the antihypertensive options already included in the Model List, such as monotherapies and dual combinations. Their inclusion aims to expand treatment choices in countries that have the capacity to manage antihypertensive medicines through robust supply chains, procurement systems and national guidelines, which define the appropriate use of different classes and their combinations. The Committee noted that these formulations do not represent new medicines, but rather combinations of active pharmaceutical ingredients already recommended in the Model List. The Committee noted that cost comparisons of fixed-dose combinations with the sum of the component monotherapies varied across settings and stressed the need for national decision-makers to take favourable differential price into consideration when making national selection decisions. The Committee also reiterated the importance of the continued availability of single-agent antihypertensives to allow the provision of monotherapy when indicated and treatment modification when required.
Contexte
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Triple fixed-dose combinations of antihypertensive medicines have not been previously evaluated for inclusion on the EML for the treatment of essential hypertension. In 2019, the Expert Committee recommended the addition of four dual fixed-dose combinations (lisinopril + amlodipine, lisinopril + hydrochlorothiazide, telmisartan + amlodipine and telmisartan + hydrochlorothiazide) to the core list of the EML for the treatment of essential hypertension. Listing was recommended with square boxes for each component, indicating that other medicines within the respective pharmacological classes represent therapeutic alternatives. The Committee accepted the efficacy of fixed-dose combination antihypertensives compared with placebo or monotherapy for reducing blood pressure and cardiovascular events but expressed concern that the application did not provide strong evidence of the claimed advantages of fixed-dose combination therapy versus dual component monotherapy. However, the Committee accepted that many patients require multiple antihypertensive treatments to achieve blood pressure targets and recognized that fixed-dose

combinations may confer advantages for patients over single medicines given concomitantly in terms of greater adherence and a reduced pill burden. The Committee considered that the ongoing availability of single-agent antihypertensive medicines was critical to allow treatment modification where necessary and that fixed-dose combinations should not displace single components at the country level. The Committee also noted that the availability of multiple fixed-dose combinations in varying strengths may be associated with significant supply chain and affordability issues in low- and middle-income countries. The Committee noted that the cost of fixed dose combinations varied in different settings and was not always the same as, or lower than, the sum of the cost of the corresponding component monotherapies. The Committee stressed that the cost of fixed-dose combinations should not be significantly higher than the sum of the cost of their component monotherapies and that the opportunity costs associated with treating patients with fixed-dose combinations must be considered, particularly in resource-constrained settings where access is limited (1).

Pertinence pour la santé publique

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The public health relevance of effective treatments for hypertension is well established and accepted. Hypertension, defined as blood pressure of 140/90 mmHg or higher, is an important global health issue, affecting about 1.4 billion people worldwide. Despite the availability of effective treatments, globally, only one in five individuals with hypertension has their blood pressure adequately controlled, with lower rates reported in low- and middle-income countries. Globally, about one in every three adults (aged 30–79 years) lives with hypertension. The prevalence of hypertension is greater than 25% in most countries, including low- and middle-income countries (2). Hypertension is a leading risk factor for cardiovascular diseases including heart attacks, strokes and heart failure (3).

Bénéfices

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Systematic reviews and meta-analyses Triple versus dual combination therapy The applicants conducted a systematic review and meta-analysis of 19 randomized controlled trials (16 322 participants) that compared triple versus dual combinations of antihypertensive medicines over 4 to 12 weeks. Outcome measures reported were systolic and diastolic blood pressure reduction and the proportion of patients achieving blood pressure control. Average baseline blood pressure was 162/99 mmHg in untreated patients and 150/94 mmHg in those uncontrolled on dual therapy. The results reported in the application found high-certainty evidence of significant reductions favouring triple combination therapy in systolic blood pressure (−5.4 mmHg (95% confidence interval (CI) −4.7 mmHg to −6.2 mmHg; P < 0.001; 18 randomized controlled trials, 14 372 participants), and diastolic blood pressure (−3.2 mmHg, 95% CI −2.6 mmHg to −3.7 mmHg; P < 0.001; 18 randomized controlled trials, 14 372 participants) and a greater proportion of participants achieving blood pressure control (66.8% versus 50.2%, rate ratio (RR) 1.3, 95% CI 1.2 to 1.4; P < 0.001; 13 randomized controlled trials, 11 274 participants). Fixed-dose combination therapy versus free equivalent combination therapy A 2021 systematic review and meta-analysis of 44 randomized and non-randomized studies assessed whether fixed-dose combination therapy improved adherence, persistence and blood pressure control compared with free equivalent combination therapy in patients with hypertension (4). A narrative analysis was performed for the outcomes of adherence and persistence, while a meta-analysis was done for blood pressure reductions. For adherence, 18/23 (78.3%) studies showed significantly improved adherence with fixed-dose combinations compared with free equivalent combination therapy. For persistence, 14/16 (87.5%) studies showed significantly improved persistence or lower discontinuation rates with fixed-dose combinations compared with free equivalent combination therapy. Fixed-dose combination therapy resulted in significant reductions in systolic (mean difference (MD) −3.99 mmHg, 95% CI −7.92 mmHg to −0.07 mmHg; P = 0.05) and diastolic blood pressure (MD −1.54mmHg, 95% CI −2.67 mmHg to −0.41 mmHg; P = 0.0076) compared with free equivalent combination therapy at week 12. Low-dose combination therapy versus usual care A 2023 systematic review and meta-analysis of seven randomized controlled trials (1918 participants) assessed the efficacy and safety of low-dose combination therapy consisting of three or four antihypertensive medicines compared to monotherapy, usual care or placebo (5). Pooled results for the primary outcome of mean reduction in systolic blood pressure showed significant differences favouring combination therapy at 4 to 12 weeks compared with active comparators (difference in means 7.4 mmHg, 95% CI 4.3 mmHg to 10.5 mmHg; P < 0.001; five randomized controlled trials) and placebo (difference in means 18.0 mmHg, 95% CI 15.1 mmHg to 20.8 mmHg; P < 0.001; four randomized controlled trials). Low-dose combination therapy was also associated with a greater reduction in systolic blood pressure at 6–12 months follow-up compared with active comparator (MD 6.4 mmHg, 95% CI 1.18 mmHg to 11.0 mmHg; P = 0.06; two randomized controlled trials). For the secondary outcome of the proportion of patients achieving blood pressure control (< 140/90 mmHg) at 4 to 12 weeks, pooled results significantly favoured combination therapy compared with active comparators (risk ratio (RR) 1.48, 95% CI 1.34 to 1.64; P < 0.001; five randomized controlled trials) and placebo (RR 3.03, 95% CI 1.93 to 4.77; P < 0.001; three randomized controlled trials). Individual trials Low-dose combination therapy versus usual care The applicants identified four randomized controlled trials (1648 participants) that compared low-dose fixed-dose combination versus usual care in the treatment of hypertension: TRIUMPH (6), QUARTET (7), QUARTET USA (8) and VERONICA (9). Upfront use of low-dose combination therapy achieved significantly greater reductions in systolic blood pressure than usual care at first to final follow up visit in TRIUMPH (MD at 6 months −9.8 mmHg, 95% CI −7.9 mmHg to −11.6 mmHg; P < 0.001), QUARTET (MD at 12 months −7.7 mmHg, 95% CI −5.2 mmHg to −10.3 mmHg; P < 0.001) and VERONICA (MD at 6 months −4.5 mmHg, 95% CI −0.09 mmHg to −8.1 mmHg; P < 0.001). In QUARTET USA, the reduction in systolic blood pressure favoured low-dose combination therapy but the difference was not significant (MD at 6 months −4.8 mmHg, 95% CI 1.3 mmHg to −10.8 mmHg; P = 0.123). The application reported that at final follow-up visit, blood pressure control (< 140/90 mmHg) was achieved in a greater proportion of participants receiving low-dose combination therapy than usual care (80% versus 65%, RR 1.22, 95% CI 1.14 to 1.30). Triple versus dual combination therapy An international, randomized, double-blind, active-controlled trial compared the efficacy and safety of a low-dose fixed-dose combination of telmisartan 20 mg + amlodipine 2.5 mg + indapamide 1.25 mg with each possible dual combination of its components (10). After a 4-week active run-in period, participants (n = 1385) were randomized 2:1:1:1 to continued half-dose fixed-dose combination, or half-dose telmisartan + amlodipine, or telmisartan + indapamide or amlodipine + indapamide. Doses were doubled at 6 weeks, except in cases of clinical contraindication. The primary efficacy outcome was the mean change in home systolic blood pressure from baseline to week 12. The results showed that at week 12, the difference in systolic blood pressure was significantly lower in the triple fixed-dose combination group than in each dual combination group with least-squares differences of: −2.5 mmHg (95% CI −3.7 mmHg to −1.3 mmHg) versus telmisartan + indapamide; −5.4 mmHg (95% CI

−6.8 mmHg to −4.1 mmHg) versus telmisartan + amlodipine; and −4.4 mmHg (95% CI −5.8 mmHg to −3.1 mmHg) versus amlodipine + indapamide. Significant differences in home diastolic blood pressure, and clinical systolic and diastolic blood pressure favouring the triple fixed-dose combination group were also reported. Improvements in blood pressure control rates favouring the triple fixed-dose combination were also seen for all comparisons.

Torts

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From the systematic review performed by the applicants that compared triple versus dual combination antihypertensive therapy, there was low-certainty evidence of increased risks with triple combination therapy of any adverse event (46.8% versus 36.4%, RR 1.7, 95% CI 1.5 to 2.0; < 0.0001; 18 randomized controlled trials, 13 989 participants), and treatment-related adverse events (20.7% versus 15.3%, RR 1.7, 95% CI 1.4 to 1.9; P < 0.0001; 17 randomized controlled trials, 13 925 participants). There was very-low-certainty evidence of an increased risk of withdrawal due to adverse events associated with triple combination therapy (4.0% versus 3.0%, RR 1.4, 95% CI 1.2 to 1.7; P < 0.0001; 16 randomized controlled trials, 13 391 participants. In the randomized controlled trial comparing low-dose fixed-dose combination of telmisartan 20 mg + amlodipine 2.5 mg + indapamide 1.25 mg with each possible dual combination of its components, withdrawal due to adverse events were not significantly different between treatment groups, occurring in 2.0%, 1.4%, 1.1% and 1.4% of participants in the triple combination, telmisartan + indapamide, telmisartan + amlodipine and amlodipine + indapamide groups, respectively. The proportions of participants with a serious adverse were 3.1%, 2.5% 2.1% and 2.2%, in the four treatment groups, respectively. The most commonly reported adverse events were generally mild and included dizziness and peripheral (10). The application described predefined subgroup analyses of the TRIUMPH, QUARTET, QUARTET USA and VERONICA trials. No significant differences were reported between the low-dose combination and usual care groups in withdrawals due to adverse events, serious adverse events, dizziness or symptomatic hypotension, headache, musculoskeletal pain, gastrointestinal discomfort or peripheral oedema. In the TRIUMPH trial, adverse events were reported in 38.1% and 34.8% of participants in the triple combination (telmisartan 20 mg + amlodipine 2.5 mg + chlorthalidone 12.5 mg) and usual care groups, respectively. The most commonly reported adverse events were musculoskeletal pain (6.0% and 8.0%, respectively) and dizziness, presyncope or syncope (5.2% and 2.8%, respectively). No significant differences were seen between treatment groups in withdrawals due to adverse events (6.6% versus 6.8%) (6). In the VERONICA trial, adverse events of special interest were reported in 2% and 3% of participants in the triple combination protocol group (quarter, half and standard doses of telmisartan + amlodipine + indapamide) and usual care groups, respectively. No discontinuations due to adverse events were reported in either group (9). The 2023 systematic review reported that low-dose combination therapy was associated with higher rates of dizziness compared with active comparators (14% versus 11%, RR 1.28, 95% CI 1.00 to 1.63) but not for peripheral oedema, headache, musculoskeletal pain or serious adverse events. No significant difference was seen between treatment groups for withdrawals due to adverse events (5% versus 4%, RR 1.14, 95% CI 0.71 to 1.82) (5).

Rapport coût/efficacité

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A cost analysis from the India Hypertension Control Initiative showed that the procurement prices of fixed-dose combinations are comparable to those of individual pills in the public sector (11). A 2020 study compared prices of antihypertensive fixed-dose combinations and single component pills in equivalent doses in the private health-care sector in India (12). Three triple fixed-dose combinations were included in the analysis (two with different doses of amlodipine + telmisartan + hydrochlorothiazide and one with amlodipine + olmesartan + hydrochlorothiazide). Prices for the fixed-dose combinations were consistently higher than the sums of their components. In a report developed by Resolve to Save Lives in collaboration with the Médecins Sans Frontières Access Campaign to identify barriers to affordable antihypertensive medicines in low- and middle-income countries, fixed-dose combinations were cheaper than the separate agent equivalents in the private sector in countries with larger domestic manufacturing capacity, i.e. Brazil, Philippines and South Africa. However, the reverse was true for countries with smaller domestic pharmaceutical market, such as Lebanon and Nigeria (13). The application presented a summary of retail prices of the proposed fixed-dose combinations in private markets in India, Kenya, Nigeria and Philippines. Prices showed considerable variability by country. For example, 1 months' supply of valsartan 160 mg + amlodipine 10 mg + hydrochlorothiazide 12.5 mg was 3.61 United States dollars (US$) in India, US$ 37.30 in Kenya, US$ 28.86 in Nigeria and US$ 13.80 in Philippines. A 2019 study conducted a within-trial (6 month) and modelled (10 year) economic evaluation of the TRIUMPH from the Sri Lankan health-system perspective (14). Incremental cost-effectiveness ratios were calculated to estimate the cost per additional participant achieving target blood pressure at 6 months and cost per disability adjusted life year (DALY) averted over 10 years. Using a fixed-dose combination cost of US$ 0.16 per day based on the price of a fixed-dose combination for hypertension in India, the study reported a cost per participant reaching target blood pressure at 6 months of US$ 7.93 (95% CI US$ 6.59 to 11.84) and an incremental cost-effectiveness ratio of US$ 2842.79 (95% CI US$ −28.67 to 7514.24) per DALY averted over 10 years. In sensitivity analyses, incremental cost-effectiveness ratios were most sensitive to the price of the fixed-dose combination. The fixed-dose combination strategy was considered likely to be cost-effective at willingness-to-pay thresholds ≥ US$ 6100 per DALY averted. A 2011 meta-analysis of 12 retrospective database studies compared health-care resource use costs, adherence and persistence between groups of patients taking antihypertensive medicines as fixed-dose combinations versus free-equivalent components (15). Pooled analysis of annual health-care costs reported significantly lower costs for fixed-dose combinations (mean difference ¬US$ −1357.01, 95% CI US$ −1935.49 to −778.53; seven studies, 44 336 participants). A 2013 retrospective cost analysis evaluated the economic impact of switching to fixed-dose combination antihypertensive therapy from angiotensin-receptor blocker-based antihypertensive treatment using pharmacy claims data in Japan (16). The study reported that switching to fixed-dose combination treatment was associated with an annual saving of US$ 112.00 for patients in their costs for antihypertensive medicines. However, it was noted that in about 20% of patients who switched from angiotensin-receptor blocker monotherapy to fixed-dose combination therapy, the medicine costs increased by US$ 25.50. A 2009 study estimated the potential cost-savings from switching patients from angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker and thiazide diuretic antihypertensive treatment as separate agents to fixed-dose combination treatment from the health-system perspective in Canada (17). Based on a conversion of 60–100% of patients to fixed-dose combination products, the estimated potential cost savings were Canadian$ 27 to 45 million a year.

Directives de l'OMS

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The 2021 WHO guidelines for the pharmacological treatment of hypertension in adults includes a strong recommendation for the use of thiazide and thiazide-like diuretics, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, or long-acting dihydropyridine calcium channel blockers as initial treatment for adults with hypertension requiring pharmacological treatment (high-certainty evidence). The guidelines also include a conditional recommendation for combination therapy, preferably with a single-pill combination (to improve adherence and persistence) as initial treatment in adults with hypertension requiring pharmacological treatment and they recommend that the medicines used in combination be chosen from the above-mentioned medicine classes (moderate-certainty evidence) (3).

Disponibilité

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The application provide a summary of a sample of countries/regions in which valsartan + amlodipine + hydrochlorothiazide, perindopril + amlodipine + indapamide, and olmesartan + amlodipine + hydrochlorothiazide products are available. The fixed-dose combinations are variably available in Argentina, Australia, Europe, India, Kenya, Mexico, Nigeria, Philippines and the United States of America. It was reported that telmisartan + amlodipine + indapamide is not currently available in any country; however, regulatory applications are under review or planned for 2025 in different settings.

Autres considérations

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The Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The department supported the inclusion of triple fixed-dose combination antihypertensive on the EML. However, it highlighted the need to assess the implications of introducing these formulations for national procurement systems, including potential benefits from reduced logistics and inventory complexity versus the upfront costs of transitioning to a new medication. Consideration has to be given to negotiating bulk purchasing agreements, ensuring generic availability and integrating fixed-dose combinations into existing essential medicines lists to optimize affordability and sustainability within constrained health budgets. The department also considered that the inclusion of these formulations on the EML could catalyse wider adoption, stimulate competition to lower prices and enhance access in resource-constrained health systems.

□ Afficher les références Masquer les références

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; https://apps.who.int/iris/handle/10665/330668). 2. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398(10304):957-80 (https://doi.org/10.1016/s0140-6736(21)01330-1). 3. Guideline for the pharmacological treatment of hypertension in adults. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/344424). 4. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to Single-Pill Versus Free-Equivalent Combination Therapy in Hypertension: A Systematic Review and Meta-Analysis. Hypertension. 2021;77(2):692-705 (https://doi.org/10.1161/hypertensionaha.120.15781). 5. 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 Cardiology. 2023;8(6):606-11 (https://doi.org/10.1001/jamacardio.2023.0720). 6. 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;320(6):566-79 (https://doi.org/10.1001/jama.2018.10359). 7. 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. Lancet. 2021;398(10305):1043-52 (https://doi.org/10.1016/s0140-6736(21)01922-x). 8. 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;47(6):1668-77 (https://doi.org/10.1038/s41440-024-01658-y). 9. 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 (https://doi.org/10.1001/jama.2024.18080). 10. Rodgers A, Salam A, Schutte AE, Cushman WC, de Silva HA, Di Tanna GL et al. Efficacy and safety of a novel low-dose triple single-pill combination of telmisartan, amlodipine and indapamide, compared with dual combinations for treatment of hypertension: a randomised, double-blind, active-controlled, international clinical trial. Lancet. 2024;404(10462):1536-46 (https://doi.org/10.1016/s0140-6736(24)01744-6). 11. Sahoo SK, Pathni AK, Krishna A, Sharma B, Cazabon D, Moran AE et al. Financial implications of protocol-based hypertension treatment: an insight into medication costs in public and private health sectors in India. J Hum Hypertens. 2023;37(9):828-34 (https://doi.org/10.1038/s41371-022-00766-x). 12. Negi S, Neupane D, Sahoo SK, Mahajan T, Swaroop K, Moran AE et al. Prices of combination medicines and single-molecule antihypertensive medicines in India's private health care sector. J Clin Hypertens (Greenwich). 2021;23(4):738-43 (https://doi.org/10.1111/jch.14143). 13. Under Pressure: Strategies to improve access to medicines to treat high blood pressure in low- and middle-income countries. Resolve to Save Lives, 2022 (https://resolvetosavelives.org/wp-content/uploads/2023/09/RTSL-Under-Pressure-1.pdf). 14. Lung T, Jan S, de Silva HA, Guggilla R, Maulik PK, Naik N et al. Fixed-combination, low-dose, triple-pill antihypertensive medication versus usual care in patients with mild-to-moderate hypertension in Sri Lanka: a within-trial and modelled economic evaluation of the TRIUMPH trial. Lancet Glob Health. 2019;7(10):e1359-e66 (https://doi.org/10.1016/s2214-109x(19)30343-2). 15. Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. J Clin Hypertens (Greenwich). 2011;13(12):898-909 (https://doi.org/10.1111/j.1751-7176.2011.00550.x). 16. Akazawa M, Fukuoka K. Economic impact of switching to fixed-dose combination therapy for Japanese hypertensive patients: a retrospective cost analysis. BMC Health Serv Res. 2013;13:124 (https://doi.org/10.1186/1472-6963-13-124). 17. Stankus V, Hemmelgarn B, Campbell NR, Chen G, McAlister FA, Tsuyuki RT. Reducing costs and improving hypertension management. Can J Clin Pharmacol. 2009;16(1):e151-5.