Acetylsalicylic acid + atorvastatin + ramipril

Essential medicine status

ATC codes: C10BX06

Indication	Cerebral ischaemic stroke ICD11 code: 8B11
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 100 mg + 20 mg + 2.5 mg ; 100 mg + 20 mg + 5 mg ; 100 mg + 20 mg + 10 mg ; 100 mg + 40 mg + 2.5 mg ; 100 mg + 40 mg + 5 mg ; 100 mg + 40 mg + 10 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	Medicines within the same pharmacological class can be used
Therapeutic alternatives limitations	Therapeutic alternatives are Fluvastatin, lovastatin, pravastatin, simvastatin (for atorvastatin) and medicines in the 4th level ATC chemical subgroups: C09AA ACE inhibitors, plain (for ramipril)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Acetylsalicylic acid + atorvastatin + ramipril
DrugBank	Acetylsalicylic acid, Atorvastatin, Ramipril

Expert Committee recommendation

The Expert Committee acknowledged the substantial public health burden of cardiovascular disease, primarily ischaemic heart disease and stroke, which continues to rise in many settings and is the leading cause of death globally. The Committee noted that the current use of medicines to prevent and control atherosclerotic cardiovascular disease, including antiplatelet therapy and cholesterol- and blood pressure-lowering medicines, has remained low over the past 2 decades, despite high-quality evidence of their benefits as separate medicine classes. The Committee considered that small, incremental effects on cardiovascular outcomes and mortality are relevant from a public health perspective as when applied to the global population these benefits can be substantial. The Committee recalled the previous applications for inclusion of fixed-dose combinations and commended the efforts of scientists and policy-makers around the world in accumulating evidence to better understand the merits of these formulations in primary and secondary prevention of cardiovascular disease. The Committee considered that the totality of the evidence presented both previously and built upon in the current application was substantial, including multiple large randomized trials, and demonstrated that fixed-dose combination therapy reduced the risk of fatal and non-fatal major cardiovascular adverse events. The Committee also noted that the available data indicate that fixed-dose combination therapy was associated with improvements in adherence and quality of life. The Committee noted the concerns expressed by previous Expert Committees about cost and cost–effectiveness and considered that these concerns had been satisfactorily addressed, noting that fixed-dose combination therapy has been found to be cost-effective in multiple studies, and also noting the increasing availability of generic formulations in several countries and improved affordability. The Committee considered that the cost of fixed-dose combinations should be equal to or ideally lower than the sum of the corresponding component monotherapies. The Committee considered that the fixed-dose combinations could be proposed for WHO prequalification to ensure that products met acceptable standards of quality, safety and efficacy. This process could facilitate access in low- and middle-income countries where national regulatory capacity may be lacking. The Committee considered potential risks associated with using fixed-dose combination therapy as initial treatment instead of multiple component monotherapy and

noted the need to be able to adjust doses and in some cases to tailor treatment to individual patients depending on comorbidities, contraindications and other individual patient factors. The Committee therefore emphasized that the ongoing availability of single agent cardiovascular medicines was critical to allow treatment modification where necessary, and that combination products should not displace single components at the country level. The Committee commended the efforts of WHO in developing the HEARTS technical package for cardiovascular disease management and the guidelines for pharmacological treatment of hypertension. The Committee recommended that WHO evaluate the potential benefits of developing guidance specific for the clinical use and national implementation of fixed-dose combinations for cardiovascular disease prevention to supplement existing guidance and support health professionals prescribing these formulations. Based on these considerations, the Expert Committee recommended the inclusion of the three fixed-dose combinations of cardiovascular medicines (acetylsalicylic acid + simvastatin + ramipril + atenolol + hydrochlorothiazide; acetylsalicylic acid + atorvastatin + ramipril; and atorvastatin + perindopril + amlodipine) on the core list of the EML for use in the primary and secondary prevention of atherosclerotic cardiovascular diseases. Components of the combinations should be listed with a square box, indicating other medicines within the respective pharmacological classes represent therapeutic alternatives, consistent with the current square box listings for hydrochlorothiazide, antihypertensive medicines and statins.

Background

Applications for the inclusion of various fixed-dose combination formulations of medicines for secondary prevention of atherosclerotic cardiovascular disease in adults had previously been considered by the Expert Committee in 2013, 2015 and 2017. On each occasion, listing was not recommended. Refer to the corresponding technical reports from each meeting for more information (1–3). The current application builds on the evidence presented in the previous applications. The medicines included in the fixed-dose combinations formulations proposed in the current application are all already included individually on the EML.

Public health relevance

Cardiovascular diseases, primarily ischaemic heart disease and stroke, are the leading cause of death worldwide. Data from the Global Burden of Disease study showed that in 2019, cardiovascular diseases were responsible for an estimated 18.6 million deaths globally (an increase from 12.1 million in 1990) and constituted almost one third of all global deaths. In addition, prevalent cases of total cardiovascular diseases increased from 271 million in 1990 to 523 million in 2019. Global trends also increased for disability-adjusted life years (DALYs) and years of life lost (YLL), and years lived with disability (YLD) doubled over the same time period (4). Clinical guidelines recommend pharmacotherapy using cholesterol and blood pressure-lowering medicines for secondary prevention in individuals with prevalent disease, and for primary prevention in individuals at high risk of cardiovascular disease. Antiplatelet therapy with aspirin is also recommended for secondary prevention. Pharmacotherapy was also recommended in WHO's global action plan for the prevention and control of noncommunicable diseases 2013–2020 (5) for patients with and at high risk of cardiovascular disease. These medicines, individually and as pharmacological classes have long been included in the Model List of Essential Medicines because of their efficacy, safety and cost–effectiveness for both prevalent cardiovascular disease patients and those at high risk of incident disease. The WHO HEARTS technical package emphasizes a risk-based approach for country-level implementation (6). Despite the availability of effective medicines, the uptake of individual medicines for cardiovascular disease prevention remains low (7). Data from 40 demographic health surveys in low- and middle-income countries (2013–2019) show that less than 10% of eligible adults use recommended pharmacotherapy (statins, blood pressure-lowering medicines and aspirin) for primary or secondary prevention of cardiovascular disease (8,9). Low rates of use are also reported in high-income countries. For example, in the United States, data indicate that one out of every four adults with prevalent cardiovascular disease takes the combination of antiplatelet, statin and blood pressure-lowering therapy for secondary prevention of atherosclerotic cardiovascular disease (10,11). The longitudinal rates of medication use as secondary prevention for cardiovascular disease were studied in the Prospective Urban Rural Epidemiology (PURE) study in 17 countries. The study spanned 12 years period and found little improvement in the use of medicines for secondary prevention of cardiovascular disease over time. This lack of change was observed in countries of all income levels (7).

Benefits

A systematic review by the applicants builds on a 2017 Cochrane systematic review of fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases (13 randomized controlled trials, 9059 participants) (12). The applicant's review included data from an additional 13 clinical trials (18 277 participants). Among these new trials, three (PolyIran (13), TIPS-3 (14) and SECURE (15)) published in the past 3 years have contributed to strengthening the evidence for fixed-dose combination therapy. In total, the evidence presented for fixed-dose combination therapy includes 26 trials (27 336

participants). Details of the included studies are presented in the application. Control groups in the trials included placebo, usual care and individual medicine monotherapy. Primary prevention Based on study level meta-analyses, fixed-dose combination therapy was associated with a 29% reduction in the risk of fatal and non-fatal major adverse cardiovascular events (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.63 to 0.79; five randomized controlled trials, high-quality evidence) and an 11% reduction in the risk of all-cause mortality (5.6% versus 6.3%; RR 0.89, 95% CI 0.78 to 1.00; four randomized controlled trials; high-quality evidence) compared with control. Based on study-level meta-analyses, fixed-dose combination therapy was associated with significant reductions in risk factors, including a decrease in systolic blood pressure (weighted mean difference (MD) –8.08 mmHg, 95% CI –10.83 to –5.34 mmHg; 17 randomized controlled trials; high-quality evidence) and low-density lipoprotein cholesterol (weighted MD –1.06 mmol/L, 95% CI –1.36 to -0.76 mmol/L; 16 randomized controlled trials; high-quality evidence). These findings are supported by data from an individual participant data meta-analysis of three outcome-driven primary prevention trials comparing a fixed-dose combination treatment strategy versus placebo or usual care (PolyIran (13), TIPS-3 (14) and HOPE-3 (16)) conducted by the Polypill Trialists' Collaboration. The results showed a 38% overall reduction in the risk of cardiovascular death, myocardial infarction, stroke, or arterial revascularization with fixed-dose combination therapy (3.0% versus 4.9%, hazard ratio (HR) 0.62, 95% CI 0.53 to 0.73). The results were consistent for fixed-dose combinations that included aspirin (2.6% versus 4.8%; HR 0.53, 95% CI 0.41 to 0.67) and did not include aspirin (3.3% versus 4.9%; HR 0.68, 95% CI 0.57 to 0.81). The meta-analysis also found fixed-dose combination therapy to be associated with reductions in systolic blood pressure (mean difference –4.7 mmHg, 95% CI –4.2 to –5.2 mmHg) and low-density lipoprotein cholesterol (mean difference –0.59 mmol/L, 95% CI –0.55 to –0.62 mmol/L). Additionally, there was no evidence of heterogeneity across tertiles of baseline predicted risk levels or other characteristics (17). Secondary prevention The SECURE trial was a randomized phase III trial (2499 participants) that assessed fixed-dose combination therapy with aspirin + ramipril + atorvastatin versus usual care in patients with myocardial infarction within the previous 6 months (15). Fixed-dose combination therapy was associated with a 24% relative risk reduction for the primary composite outcome of cardiovascular death, non-fatal type 1 myocardial infarction, non-fatal ischaemic stroke or urgent revascularization (9.5% versus 12.7%; HR 0.76, 95% CI 0.60 to 0.96) compared with usual care. For the secondary outcome of a composite of cardiovascular death, non-fatal type 1 myocardial infarction, or non-fatal ischaemic stroke, there was a 30% relative risk reduction associated with fixed-dose combination therapy (8.2% versus 11.7%; HR 0.70, 95% CI 0.54 to 0.90). The reductions in cardiovascular disease events were likely due to improvements in adherence, as the fixed-dose combination therapy group showed higher adherence rates (74.1% versus 63.2% at 24 months; RR 1.17, 95% CI 1.10 to 1.25). The PolyIran trial included 737 participants with cardiovascular disease at baseline. Fixed-dose combination therapy was associated with a reduced rate of major adverse cardiovascular events in this subgroup, similar in direction and magnitude to the overall trial results, with no evidence of an interaction based on baseline disease status (adjusted HR 0.80, 95% CI 0.57 to 1.12, Pinteraction = 0.19) (13). The application stated that other trials with at least 15% of participants with prevalent cardiovascular disease showed substantial heterogeneity with results likely being driven by the small number of events from trials that were not designed to evaluate the effect of fixed-dose combination therapy on clinical outcomes. These results were not determined to be reliable and therefore estimates for secondary prevention were derived exclusively from secondary prevention populations reported in the SECURE and PolyIran trials. Mixed primary and secondary prevention A meta-analysis of trials in mixed primary and secondary prevention showed that fixed-dose combination therapy resulted in a reduction in risk factors compared with usual care, including systolic blood pressure (weighted MD –1.23 mmHg, 95% CI –2.10 to –0.36 mmHg, seven randomized controlled trials, high-quality evidence) and low-density lipoprotein cholesterol (weighted MD 0.02 mmol/L, 95% CI –0.06 to 0.03 mmol/L, seven randomized controlled trials, moderate-quality evidence). The applicants concluded that overall, the expected benefits of fixed-dose combination therapy in a general population would be greater due to the reported low baseline treatment rates. Health-related quality of life Health-related quality of life showed no significant differences between treatment groups in EQ-5D scores (MD 0.22, 95% CI –1.02 to 1.46, three randomized controlled trials, 2109 participants). Adherence Patients randomized to fixed-dose combination therapy had higher adherence rates than controls (RR 1.16, 95% CI 1.03 to 1.29, 11 randomized controlled trials). However, there was considerable heterogeneity in this outcome, making it difficult to assess the true effect on adherence, especially in an unselected population where adherence rates might differ from clinical trial participants who usually have higher adherence rates than the general population. Evidence in different populations and settings Data from the SECURE trial showed no evidence of heterogeneity of effect based on country (although SECURE included data only from high-income European countries) (15). The HOPE-4 cluster randomized trial (30 clusters, 1371 participants) also showed the feasibility, effectiveness and safety of delivering the combination of angiotensin receptor blocker + statin in patients without prior cardiovascular disease through non-physician health workers in Colombia and Malaysia (18). These health workers were supported by computer-based simplified management algorithms. The intervention resulted in a 43% relative risk reduction in predicted risk (–6.4%, 95% CI –8.0% to –4.8%) in the control group and –11.2%, 95% CI –12.9% to –9.5%) in the intervention group, which were driven by greater reductions in systolic blood pressure (–11.5 mmHg, 95% CI –14.9 to –8.0 mmHg) and low-density lipoprotein cholesterol (–0.41 mmol/L, 95% CI –0.6 to –0.2 mmol/L). Implementation of the combination of aspirin + ramipril + atorvastatin has also been shown to be feasible and acceptable in patients with prevalent

cardiovascular disease in a humanitarian setting in Lebanon (19). A 2022 meta-analysis of 16 randomized trials (26 567 participants) evaluated the efficacy of fixed-dose combination therapy versus placebo or usual care as primary or secondary prevention of cardiovascular disease (20). This review included, a subgroup analysis based on country income level which showed that in low- and middle-income countries, fixed-dose combination therapy was associated with lower rates of major adverse cardiovascular events (RR 0.67, 95% CI 0.56 to 0.79) compared with high-income countries (RR 1.04, 95% CI 0.69 to 1.58). This difference is likely influenced by the background treatment rate of the comparator group.

Harms

In primary prevention trials, fixed-dose combination therapy was shown to increase the risk of any adverse event by 21% compared with controls (11.6% versus 9.6%; RR 1.21, 95% CI 1.12 to 1.31; 15 randomized controlled trials; high-quality evidence). The applicants proposed that this may be a result of increased exposure to these medicines as a result of improved adherence. Most adverse events associated with fixed-dose combination therapy were mild and reversible, and were consistent with the known adverse events of the individual medicines (e.g. dizziness and muscle pain). The findings from the individual participant data meta-analysis, which focused on patients with a primary prevention indication, support these results (17). In secondary prevention trials, fixed-dose combination therapy increased the risk of adverse events by 7% (27.5% versus 25.9%; RR 1.07, 95% CI 0.99 to 1.15; eight randomized controlled trials; moderate-quality evidence). The quality of evidence was downgraded because of heterogeneity and the true effect may be influenced by the treatment rate in the comparator group. Data from the SECURE trial of secondary prevention showed no significant difference in adverse events between the fixed-dose combination therapy group and the usual care group (15). Discontinuation rates were similar between groups in the nine trials that reported this outcome (RR 1.05%, 95% CI 0.99 to 1.11). The proposed fixed-dose combinations are contraindicated in pregnant or breastfeeding women, following the contraindications of the individual components.

Cost / cost effectiveness

The application included the results of a survey to collect primary data on market authorization, retail prices and affordability of fixed-dose combinations in 12 countries (Argentina, Bangladesh, Cameroon, Colombia, India, Iraq, Mauritius, Mexico, Nepal, Nigeria, Spain and Sweden). Fixed-dose combinations were stocked by private pharmacies in Argentina, India, Mauritius and Spain. None of the public pharmacies visited stocked any combination. Affordability was determined based on the WHO/Health Action International standards, which consider a medicine to be affordable if the cost of 1 month’s supply is lower than the lowest daily wage of a government worker in that area. The findings are presented in Table 22 (refer TRS 1049). A 2020 systematic review analysed 24 studies that evaluated the cost–effectiveness of fixed-dose combinations for primary and secondary prevention of cardiovascular disease (30). Most of the included studies were conducted in European countries, with three conducted in Asia. Four multicountry studies were conducted. Three quarters of the studies analysed cost–effectiveness from a health care perspective, and the remainder from payer or societal perspectives. Across all studies, incremental cost–effectiveness ratios ranged from US$ 24 to US$ 31 000. Fourteen studies investigated fixed-dose combination therapy as primary prevention. The systematic review found that fixed-dose combination therapy was considered cost-effective in five studies, including two in which it was determined to be dominant (i.e. more effective and cost-saving). In two studies, fixed-dose combination therapy was dominated (i.e. less effective and higher cost) or not cost-effective. Twelve studies investigated fixed-dose combination therapy as secondary prevention. The review found that fixed-dose combination therapy was cost-effective in six studies, and dominant in a further four studies compared with usual care with multiple monotherapies. One study concluded that fixed-dose combination therapy was not cost-effective. A study in which fixed-dose combination therapy was compared with no treatment found the intervention to be cost-effective. The key determinants of cost–effectiveness for fixed-dose combination therapy were the price of the combination, followed by the effect of age and the risk for cardiovascular disease. A 2021 economic analysis based on the International Polycap Study 3 (TIPS-3) examined the cost implications of fixed-dose combinations as a primary prevention strategy (31). Over the 4.6 years of the trial, the use of fixed-dose combinations led to a higher mean total cost per patient in lower middle- and upper middle-income countries, but it was cost-neutral (dominant) in high-income countries. The difference in costs per patient between fixed-dose combinations and placebo over the trial period was US$ 291 in lower middle-income countries, US$ 1068 in upper middle-income countries and US$ 48 in high-income countries. These variations were influenced by higher acquisition costs in low- and middle-income countries. Cost-savings from fewer procedures and hospitalizations associated with fixed-dose combination therapy were insufficient to offset acquisition costs in lower income settings. Overall, the authors considered that fixed-dose combination therapy was affordable in all income groups when estimated using monthly household capacity to pay or a threshold of 4% of the gross national income per capita. A cost–effectiveness analysis for the proposed fixed-dose combination of aspirin + atorvastatin, + ramipril versus usual care with individual monotherapies from a Portuguese payer perspective reported an incremental cost–effectiveness ratio of €5130 per life year gained for the overall population. The incremental cost–utility ratio was €5332 per quality-adjusted life year

(QALY) gained for the overall population. At a willingness-to-pay threshold of €30000 per QALY gained, the study the chance of fixed-dose combination therapy being cost-effective was 76.1% and the chance of it being cost-saving compared with usual care was 27.8% (32).

WHO guidelines

WHO guidelines The 2007 WHO pocket guidelines for assessment and management of cardiovascular risk recommends that all individuals with established coronary heart disease, cerebrovascular disease or peripheral vascular disease should receive treatment with blood pressure-lowering therapy, a statin and aspirin. Lifestyle advice should also be offered (e.g. smoking cessation, dietary changes, physical activity, weight control and alcohol intake) (21). The 2016 HEARTS technical package for cardiovascular disease management in primary care provides information on evidence-based treatment protocols and risk-based management of cardiovascular disease. These include recommendations for the use of antihypertensive therapy, statins and anti-platelet therapy (6). 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 (strong recommendation; 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 recommends that the medicines used in combination be chosen from the above-mentioned medicine classes (22). Other current clinical practice guidelines Statins and antihypertensive medicines are recommended for all individuals with a history of atherosclerotic cardiovascular disease in guidelines from various regions, including Australia (23), Brazil (24) Europe (25), Japan (26), the United States (27), and others, with additional support from the World Heart Federation (28). These medicines are also advised for individuals at high predicted risk of incident atherosclerotic cardiovascular disease, particularly those with type 2 diabetes mellitus 40 years and older (29). Antiplatelet therapy is also recommended for individuals with prevalent atherosclerotic cardiovascular disease, but there is no consensus yet on its use in primary prevention.

Availability

The application reported that the proposed fixed-dose combinations have variable authorization for marketing and are available in more than 70 countries worldwide.

Other considerations

The WHO Noncommunicable Diseases Department is in favour of including fixed-dose combinations for both primary and secondary prevention of cardiovascular diseases. Their support is based on: clear evidence of benefit; improved management of secondary prevention, especially in terms of adherence and persistence with the treatment; wide market availability globally; and generally being considered cost-effective and affordable.

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