A.45	Ticagrelor – prevention of atherothrombotic events – EML
Draft recommendation	☐ Recommended ☒ Not recommended **Justification:** WHO recognizes that mortality from cardiovascular disease (CVD), i.e. stroke and ischemic heart disease, is an area of unmet need. Reducing CVD mortality is one of its priorities. Although contemporary advances have improved control of modifiable risk factors for atherosclerosis, reduced complications associated with percutaneous coronary intervention (PCI), and decreased the risk of recurrent ischemia after acute coronary syndrome (ACS), a significant degree of residual risk remains in patients with CVD. Platelets play a central role in atherothrombosis, and therefore optimization of antiplatelet regimens may further reduce the residual burden of atherosclerosis-related morbidity and mortality. Dual antiplatelet therapy, usually with a P2Y12 receptor antagonist and aspirin, is generally recognized as a vital approach in the treatment of patients with ACS and is also considered standard therapy, particularly after PCI, according to several clinical guidelines. Clopidogrel is the first P2Y12 receptor antagonist to be used with aspirin as a prescribed dual antiplatelet therapy in an attempt to reduce the risk of myocardial infarction and stent thrombosis in patients with ST-elevation and non-ST-elevation ACS. It has been widely used worldwide for more than a decade and has been part of the EML since 2015. However, clopidogrel is a prodrug that often requires two-step hepatic metabolism and conversion, resulting in delayed appearance of metabolites in the blood and high variability in platelet inhibition among individuals. More than a third of them have minimal platelet inhibition or are "clopidogrel non-responders". Previous publications have shown that the platelet inhibition of clopidogrel is slow and not very potent. **Ticagrelor** is a direct-acting oral P2Y12 adenosine diphosphate receptor antagonist with reversibility and no catabolic activation, which may have a substantial impact on faster and greater platelet inhibition than clopidogrel. Compared with clopidogrel, ticagrelor is less likely to be influenced by CYP2C19 polymorphism. Underuse, non-adherence, or discontinuation of aspirin is not uncommon, can have a significant clinical impact. Lack of adherence to low-dose ASA ranged from approximately 10% to more than 50%, and patient-initiated discontinuation occurred in up to 30% of patients. The use of ASA (which is much less expensive) for secondary prevention of cardiovascular disease is so low that it and is a major concern for the utilisation of ticagrelor witch should be combined with aspirin in the majority of its indications. Thus, ticagrelor offers marginal advantages over an agent such as clopidogrel.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable **Comments**: CVD is the leading cause of death worldwide, with an estimated 17.9 million deaths per year. Although age-standardized CVD mortality rates decreased by 14.5% globally between 2006 and 2016, the burden of CVD remains disproportionately greater in low- and middle-income countries than in high-income countries, with more than 80% of CVD deaths occurring in low- and middle-income countries. It has been suggested that health system challenges in those countries contribute to the burden of CVD much more than risk factor levels, which remain low in low- and middle-income countries compared with high-income countries. For example, secondary prevention drugs for CVD remain unavailable and unaffordable in many of these countries. WHO supports governments in preventing, managing, and monitoring CVD by developing global strategies to reduce the incidence, morbidity, and mortality of CVD. These strategies include reducing risk factors, developing standards of care and strengthening the capacity of health systems to manage patients with CVD.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable **Comments:** Advantageous characteristics of ticagrelor have translated into beneficial clinical outcomes in patients with ACS, during extended maintenance therapy in specific high-risk populations, and after percutaneous coronary intervention, but not after coronary artery bypass surgery or in patients with peripheral arterial disease. According to the Phase III PLATO (Platelet Inhibition and Patient Outcomes) study, ticagrelor has more remarkable benefits than clopidogrel on total mortality, cardiovascular prevention, stent thrombosis, and myocardial infarction, without increasing rates of major bleeding in a large population of patients with ACS. In the PEGASUS study, ticagrelor given in two doses (90 mg or 60 mg twice daily) in combination with low-dose ASA was compared with ASA alone in patients with a history of myocardial infarction and additional risk factors for atherothrombosis. Both regimens of ticagrelor in combination with ASA were superior to ASA alone in preventing atherothrombotic events. However, no benefit was seen when ticagrelor was introduced in clinically stable patients (>2 years after the acute event), or more than 1 year after discontinuation of prior ADP receptor inhibitor therapy. Thus, several clinical management guidelines have suggested that ticagrelor may be a valid strategy and associated with superior effects to clopidogrel for P2Y12 inhibition in patients with ACS. Of note, in the PLATO study, the use of ticagrelor did not improve outcomes in patients with body weights below the sex-specific median values, and in the 1814 North American patients. Polish and Hungarian patients, who represent 21% of the trial population, provided nearly half of the data in favour of ticagrelor. When data from Poland and Hungary are excluded, ticagrelor was no longer superior to clopidogrel. Finally, when myocardial infarctions were assessed only by site investigators, ticagrelor was no longer superior to clopidogrel. In a randomized, double-blind trial comparing ticagrelor with clopidogrel in Asian patients with ACS (PHILO), ticagrelor was not superior to clopidogrel. In a peripheral arterial disease trial (EUCLID), ticagrelor was not superior to clopidogrel for the composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke after a median follow-up of 30 months. Recently, ticagrelor was compared to ASA in acute stroke or transient ischemic attack, and the results for major vascular events were similar. Real-world registries provide valuable additional data. The SWEDEHEART registry showed that ACS patients who received ticagrelor had significantly fewer events than patients who received clopidogrel. However, patients who received ticagrelor were younger (67 versus 71 years), had fewer comorbidities, including less heart failure, and had received dual antiplatelet therapy for a longer period of time than did patients who received clopidogrel. These results were also mitigated in a cohort of patients undergoing primary PCI for STEMI in the UK, with ticagrelor not associated with significant differences in mortality compared with clopidogrel at 30 days. Finally, recent evidence-based meta-analyses comparing ticagrelor and clopidogrel in the treatment of patients with ACS suggest similar efficacy and safety profiles for clopidogrel and ticagrelor. Considering ticagrelor is less likely to be influenced by metabolic activation and various drug action between individuals, it may be a valid and even more potent antiplatelet drug than clopidogrel, especially as an alternative strategy in treating

	patients with clopidogrel intolerance or resistance. Further studies are needed to identify ticagrelor high responders.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☐ No ☐ Not applicable **Comments**: Ticagrelor is associated with an increased risk of bleeding. In the PLATO trial, patients with a body mass index greater than 30 kg/m2 who received ticagrelor had more bleeding events; and there were more intracranial bleeds with ticagrelor than with clopidogrel, but no difference in fatal bleeds. The use of ticagrelor in patients with a known increased risk of bleeding must be weighed against the benefit in terms of preventing atherothrombotic events. The use of ticagrelor is contraindicated in patients with active pathologic bleeding, in those with a history of intracranial bleeding, and in patients with severe hepatic impairment. Bleeding tends to be more frequent in patients with renal dysfunction Dyspnea is another key adverse event in addition to bleeding. Dyspnea occurs in 10% to 15% of patients treated with ticagrelor. Dyspnea is usually mild to moderate in severity, most often occurring within 1 or 2 weeks of initiation of therapy and often resolving without the need to discontinue therapy. Very few events have been reported as severe (0.4%) and symptoms resolve on discontinuation of ticagrelor. Patients with asthma or chronic obstructive pulmonary disease may have an increased absolute risk of dyspnea with ticagrelor. Characteristics such as increased age and waist circumference, as well as conditions such as diabetes and chronic kidney disease have also been associated with an increased risk of developing dyspnea with ticagrelor therapy.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments:

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☐ No ☐ Not applicable **Comments:** There is little information on the cost effectiveness of ticagrelor vs clopidogrel in low- and middle-income countries. However, it appears that the few cost-effectiveness assessments have found ticagrelor to be cost-effective vs clopidogrel
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable **Comments**: Many countries even in Europe do not have access to ticagrelor
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☐ No ☐ Not applicable **Comments**: Clopidogrel is included in the WHO EML