Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

ticagrelor 60mg film-coated tablets (Brilique®) SMC No. (1224/17)

AstraZeneca UK Ltd

10 March 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ticagrelor 60mg film-coated tablets (Brilique®) is not recommended for use within NHS Scotland.

Indication under review: co-administered with acetylsalicylic acid for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction and a high risk of developing an atherothrombotic event.

A large, phase 3, randomised, double-blind study in a high risk population who had suffered a myocardial infarction in the previous one to three years demonstrated that the addition of ticagrelor to aspirin significantly reduced the risk of ischaemic events (a composite of cardiovascular death, myocardial infarction and stroke).

The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 10 April 2017

Indication

Co-administered with acetylsalicylic acid for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

Dosing Information

Ticagrelor 60mg twice daily is recommended for extended treatment for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Treatment may be started without interruption as continuation therapy after the initial one-year treatment with ticagrelor 90mg twice daily or other adenosine diphosphate (ADP) receptor inhibitor therapy in acute coronary syndrome (ACS) patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to two years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of ticagrelor beyond three years of extended treatment. If a switch is needed, the first dose of ticagrelor should be administered 24 hours following the last dose of the other antiplatelet medication.

Ticagrelor should be taken with aspirin 75 to 150mg once daily.[1]

Product availability date

March 2016

Summary of evidence on comparative efficacy

Ticagrelor is an antiplatelet agent which acts as a reversible, selective, antagonist of the $P2Y_{12}$ adenosine diphosphate (ADP) receptor, thus preventing ADP-mediated platelet activation and aggregation. It was originally licensed at a dose of 90mg twice daily in combination with aspirin for up to 12 months for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS). The marketing authorisation has been updated to include extended treatment with ticagrelor 60mg twice daily plus aspirin for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI) of at least one year and a high risk of an atherothrombotic event. Ticagrelor extended treatment can be continued without a break from the initial one-year ticagrelor (90mg twice daily) or other ADP receptor antagonist or within two years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment.[1] The submitting company has requested that SMC considers ticagrelor 60mg twice daily in combination with low dose aspirin in patients whose most recent MI occurred within the previous two years and with a maximum treatment duration of three years.

The evidence to support the extended use of ticagrelor comes from one large, randomised, double-blind phase III study (PEGUSUS-TIMI-54) in 21,162 patients with a previous MI who were considered to be at high risk of an atherothrombotic event.[2-4] The study assessed whether long-term therapy with ticagrelor plus aspirin reduced the risk of major cardiovascular events compared with aspirin alone. Eligible patients were aged at least 50 years and had had a spontaneous MI in the previous one to three years. They were defined as at high risk if they had at least one of the following: age ≥65 years; > one prior MI; multivessel cardiovascular disease; diabetes

requiring medication or chronic non-end stage renal dysfunction. Patients were randomised equally to receive ticagrelor 90mg orally twice daily, ticagrelor 60mg orally twice daily or placebo; all patients also received low dose aspirin (75 to 150mg daily). Patients were followed for up to 38 months.

The primary outcome was the composite of cardiovascular death, MI or stroke performed in the full analysis set which included all randomised patients. The study was designed to compare each dose of ticagrelor with placebo; it was event-driven and used step-wise hierarchical statistical testing. Results will only be presented in this document for ticagrelor 60mg group (licensed dose for extended treatment) and placebo. After a median follow-up of 33 months, there was a significant reduction in the risk of a primary composite outcome with ticagrelor 60mg compared with placebo in both the overall study population and in the subgroup of patients which represents the proposed positioning. Details are presented in table 1 below.

Table 1: results of composite primary outcome (and its components) in the total study population and subgroup relevant to the positioning[3-5]

	Ticagrelor 60mg twice daily		**Placebo**		**Hazard ratio (95% CI), p-value**
	no. of events	**3-year KM estimate**	**no. of events**	**3-year KM estimate**	
Overall study population	**N=7,045**		**n=7,067**		
Composite primary outcome	6.9% (487/7,045)	7.77%	8.2% (578/7,067)	9.04%	0.84 (0.74 to 0.95) p=0.004
Components:					
Cardiovascular death	2.5% (174/7,045)	2.86%	3.0% (210/7,067)	3.39%	0.83 (0.68 to 1.01) p=0.07*
MI	4.0% (285/7,045)	4.53%	4.8% (338/7,067)	5.25%	0.84 (0.72 to 0.98) p=0.03*
Stroke	1.3% (91/7,045)	1.47%	1.7% (122/7,067)	1.94%	0.75 (0.57 to 0.98) p=0.03*
Proposed positioning subgroup	**n=4,331**		**n=4,333**		
Composite primary outcome	Commercial in confidence	7.79%	Commercial in confidence	9.74%	0.77 (0.66 to 0.90) p=0.001

* following the hierarchical statistical testing, since the difference between groups for cardiovascular death was not significant, further formal statistical testing was stopped: p-values are nominal.[3, 4] KM: Kaplan Meier; CI: confidence interval; MI: myocardial infarction

Secondary outcomes were cardiovascular death (noted above under components of primary outcome in table 1) and death from any cause. Since there was no significant difference between

ticagrelor and placebo for cardiovascular death, further formal statistical testing was stopped. Nominal p-values have been reported but should be interpreted with caution.[3-5]

Death from any cause was reported in 4.1% (289/7,045) of ticagrelor 60mg patients and 4.6% (326/7,067) of placebo patients in the total study population; Kaplan Meier (KM) 3-year estimates of 4.7% and 5.2% respectively; hazard ratio (HR) 0.89 (95% CI: 0.76 to 1.04), p=0.14 (nominal). Net clinical benefit was the composite of cardiovascular death, MI, stroke and thrombolysis in myocardial infarction (TIMI) major bleeding. In the total study population, this occurred 8.3% (585/7,045) of ticagrelor 60mg patients and 8.7% (618/7,067) of placebo patients; KM 3-year estimates of 9.3% and 9.6% respectively; HR 0.95 (95% CI: 0.85 to 1.06), p=0.341 (nominal).[4]

Unpublished results were presented of further subgroup analyses of the subgroup of patients <2 years from MI with/without several of the additional risk factors specified in the licence: diabetes, previous MI and non-end stage renal dysfunction (creatinine clearance <60mL/min). However, since these were post hoc analyses and subgroups of a subgroup, they should be interpreted with caution.

Quality of life was assessed using the European Quality of Life-5 Dimensions (EQ-5D) questionnaire every six months during the study period. There were small increases in EQ-5D visual analog scale results at the end of the study compared with baseline in all treatment groups but there were no apparent differences between groups (no statistical analysis was performed).[3,4]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

During the PEGASUS-TIMI 54 study, an adverse event was reported in 76% (5,311/6,958) of ticagrelor 60mg patients and 70% (4,899/6,996) of placebo patients, and these were considered serious in 24% of patients in each group. Adverse events led to discontinuation in 16% (1,139/6,958) and 8.9% (621/6,996) of patients respectively, most commonly due to bleeding (6.2% and 1.5% respectively) and dyspnoea (4.6% and 0.8% respectively).[3]

During PEGASUS-TIMI 54, the primary safety outcome was TIMI major bleeding, defined as any intracranial bleeding, clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hb) of ≥5g/dL (or when Hb is not available, a fall in haemocrit of ≥15%) or fatal bleeding (bleeding event that directly led to death within 7 days).

The incidence of TIMI major bleeding was higher with ticagrelor 60mg than placebo in the total study population and the subgroup <2 years from MI, as detailed in the table below. The relative effect of ticagrelor on major TIMI bleeding was consistent across subgroups by age, gender, weight, race, geographic region, concurrent conditions, concomitant therapy, and medical history in the total study population.

Table 2: results of primary safety outcome and its components in the safety population[3-5]

	Ticagrelor 60mg twice daily		Placebo		Hazard ratio (95% CI), p-value
	no. of events	**3-year KM estimate**	**no. of events**	**3-year KM estimate**	
Overall study population[3, 4]	**N=6,958**		**n=6,996**		
TIMI major bleeding	1.7% (115/6,958)	2.30%	0.8% (54/6,996)	1.06%	2.32 (1.68 to 3.21) p<0.001
Intracranial haemorrhage	0.40% (28/6,958)	0.61%	0.33% (23/6,996)	0.47%	1.33 (0.77 to 2.31) p=0.31
Fatal bleeding	0.16% (11/6,958)	0.25%	0.17% (12/6,996)	0.26%	1.00 (0.44 to 2.27) p=1.00
Other major bleeding	1.2% (83/6,958)	1.6%	0.4% (25/6,998)	0.5%	3.61 (2.31 to 5.65) p<0.0001
Subgroup (patients <2 years from MI)	**N=4,279**		**n=4,287**		
TIMI major bleeding	Commercial in confidence	2.40%	Commercial in confidence	1.20%	2.05 (1.38 to 3.03)

In the total study population, commonly reported non-bleeding adverse events in the ticagrelor 60mg and placebo groups respectively were: dyspnoea (14% [987/6,958] and 5.5% [383/6,996]); renal events (2.5% [173/6,958] and 2.3% [161/6,996]); bradycardia (1.7% [121/6,958] and 1.5% [106/6,996]) and gout (1.5% [101/6,958] and (1.1% [74/6,996]).

Dyspnoea was mostly of mild or moderate severity, occurring early after starting ticagrelor treatment and led to discontinuation in 4.6% of ticagrelor 60mg patients and 0.8% of placebo patients.[3,4]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

The updated marketing authorisation for ticagrelor allows extended dual antiplatelet therapy to prevent atherothrombotic events in high risk adult patients who have had an MI at least one year previously. The submitting company has requested that SMC considers ticagrelor in patients less than two years from an MI, i.e. in adults who have had an MI one to two years previously, and are at increased risk of atherothrombotic events.

The PEGASUS-TIMI 54 study demonstrated a significant reduction in the risk of the composite outcome of MI, stroke and cardiovascular death with ticagrelor plus aspirin compared with aspirin alone in a high risk population, and the treatment effect was larger in the proposed subgroup than

in the total population. The evidence to support the proposed positioning comes from subgroup analysis for which the study was not powered. This subgroup represents 61% of the total study population. The absolute reduction in MI, stroke or cardiovascular death was small (1.3% in the total population and 1.9% in the relevant subgroup) and there was no significant reduction in cardiovascular or all-cause mortality in the total study population, stopping further statistical analysis. The treatment effect was however associated with a significantly increased risk of TIMI major bleeding. The effect of ticagrelor on the composite primary outcome, cardiovascular and all-cause mortality and net clinical benefit was larger in the proposed subgroup than in the total population.[3,4]

Subgroup analyses generally found a consistent treatment effect but results of further subgroup analyses of the proposed subgroup should be interpreted with caution. This makes it difficult to identify the high risk patients who would be most likely to benefit from treatment and be least likely to experience a bleeding event.[3,4] However, there was concern that the definition of high risk patients in the study would not represent the potentially smaller group of patients likely to be considered high risk in Scottish clinical practice.

Based on the KM three year event rates, the number needed to treat with ticagrelor 60mg instead of placebo to prevent one primary composite event is 79 patients for the total study population and 51 patients for the subgroup with MI <2 years. Similarly, the number needed to harm with ticagrelor 60mg instead of placebo to cause one TIMI major bleed is 81 patients for the total study population and 89 patients for the subgroup with MI <2 years.[3]

Significantly more ticagrelor than placebo patients discontinued study treatment (mainly due to adverse events) and discontinuation rates were higher in those aged >75 years than in younger patients. The summary of product characteristics (SPC) notes that premature discontinuation with any antiplatelet therapy, including ticagrelor, could result in an increased risk of cardiovascular death or MI due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.[1]

There may be some differences between the baseline characteristics of PEGASUS-TIMI 54 study population and patients likely to receive treatment in Scottish practice.[6] In particular, eligible patients in clinical practice compared to those in the PEGASUS-TIMI 54 study may be older (than mean age 65.3 years), include a higher proportion of women (than 24%), have a lower proportion of STEMI (than 54%) and higher proportion of NSTEMI (than 41%) and have a lower history of PCI (than 83%). There may also be differences in hypertension and diabetes and in use of additional medication (aspirin, statins, beta-blockers).[3,4]

The study population excluded patients with recent bleeding and those needing oral anticoagulation so the safety profile in terms of bleeding may be different in those at greater risk in clinical practice. The study also excluded patients with a prior stroke and some of these patients may be eligible for extended treatment in clinical practice.[3 4]

Clinical experts consulted by SMC reported that there may be some off-label extended use of clopidogrel in high risk patients. There is no directly or indirectly comparative evidence versus clopidogrel in this indication.

The addition of ticagrelor to aspirin for the longer term prevention of atherothrombotic events may reduce the risk of cardiovascular death, MI or stroke in patients considered to be at high risk. However, this benefit needs to be balanced against the significantly increased risk of TIMI major

bleeding. The SPC notes that there are limited data on the efficacy and safety of ticagrelor beyond three years of extended treatment.[1]

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing ticagrelor 60mg twice daily with aspirin to aspirin alone in patients who had an MI one to two years previously at start of treatment and who were at high risk of an atherothrombotic event. Treatment on ticagrelor 60mg was assumed to continue for up to three years. The proposed population is a subset of the licensed indication and more closely reflects the patient population considered in the key study.

The clinical data source underpinning the analysis was the PEGASUS-TIMI 54 study.[2-4] In the model, the company used data from the overall study population unless the data from the subgroup of patients relevant to the proposed positioning was materially different from the overall population. The primary outcome of the study was a composite endpoint of fatal cardiovascular events, non-fatal MIs, and non-fatal strokes. In the model, more specific secondary outcomes were also used, specifically rates of CV death, non-fatal MI, and non-fatal stroke as well as rates of adverse events.

A Markov model was used with a 40 year time horizon. The model was run as a microsimulation, using the characteristics of the PEGASUS-TIMI 54 patients for each simulation. Models were created for the risk of each event based on the study data and accounted for many patient characteristics as well as ticagrelor use. Rates of death, non-fatal MIs, and non-fatal strokes were all reduced by ticagrelor use, while rates of adverse events (major and minor bleeds, dyspnoea, and gout) were increased. Patients who have an event (other than adverse events, which cause only one-off effects) were assumed to have a permanent worsening of quality of life, increase in healthcare costs, and increase in risk of further events. These risks were especially high in the year after the event.

The utility scores were derived from quality of life surveys conducted during the PEGASUS-TIMI 54 study. Medicine costs were derived from HRG codes, weighting various codes using real-world activity, or were taken from the NICE analysis TA317, with inflation applied.

The result of the analysis was an incremental cost-effectiveness ratio (ICER) of £21,377, with the average patient receiving an additional 0.067 quality-adjusted life-years (QALYs) at an average incremental cost of £1,423. Sensitivity analysis provided in the submission reported only one one-way sensitivity analysis in which the ICER exceeded £30,000/QALY, which was an analysis where a different formula for CV death risk was used. Probabilistic sensitivity analysis reported that in 98% of scenarios the ICER was below £30,000/QALY.

The main weaknesses and uncertainties with the economic analysis are as follows:

- While the model estimates that the health gains with ticagrelor treatment outweigh the effects of adverse events in the average patient, SMC clinical experts have questioned this. Some experts commented that the net clinical benefit in practice may be marginal when weighed against the increased risk of bleeds. In addition, it is not clear that the definition of high risk used in the study reflects the definition of high risk used in clinical practice to identify patients who may benefit from longer term treatment.
- The model was based on the characteristics of patients in the PEGASUS study and does not take into account Scottish population characteristics or the differences between the

study exclusion criteria and the proposed patient group likely to be treated in practice. In particular, as the study excluded patients with recent bleeding, patients may be at greater risk of adverse events in practice. The disutility applied to bleeds may also be considered too low when compared to values used in other published studies. Additional sensitivity analysis was provided which showed a small increase in the ICER when the rate of major bleeds and the disutility associated with a major bleed were increased. However, the model assumes no difference between the treatments in the rate of fatal bleeds or ICH based on the rates observed in the study. Therefore, the higher rate of major bleeds with ticagrelor was assumed to relate specifically to non-fatal, non-ICH major bleeds and modelled as a transient event. An increase in fatal bleeds or ICH with ticagrelor, which would have a much larger impact on quality of life and costs, has not been explored in the model.

- Some evidence used in the model comes from a subgroup analysis of the study which, while pre-specified, was not something the study was powered to analyse and also was one of 31 subgroups analysed. As a result, the model estimates based on these data are uncertain and no sensitivity analysis was initially provided to test the efficacy of ticagrelor. Additional analysis was subsequently provided where the hazard ratios for first events were increased simultaneously by 1 standard deviation. In this analysis the ICER increased to £26k. In a more conservative scenario analysis where the upper 95% confidence intervals were used, the ICER increased to £42k.
- Some SMC clinical experts noted that clopidogrel is currently used off-label in high risk patients and therefore could be a comparator, while others said clopidogrel was not used. The cost-effectiveness of ticagrelor compared to off-label clopidogrel was not presented.
- The baseline risk was modelled entirely using data from the PEGASUS study, which only ran for three years but is used to model risk for the duration of the model. The baseline risk curves also show unusual trends, such as an initial increase in CV death risk with time despite the general trend in all areas that risk decreases with time after the MI. The company did support the baseline risk used by citing a published study.[6] However, this study did not look specifically at patients whose MI was less than two years ago, and the data are older which may affect generalisability. However, the company stated that the rise in risk in the model is the best fit of available data and also modelled alternate measures of long-term risk such as a constant rate, which had only a small effect on the final ICER. Additional sensitivity analysis was provided which increased the baseline risk of first events by 25% and this increased the ICER to £27k.

Due to the limitations outlined above the economic case has not been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified patient group.

- We received a patient group submission from Pumping Marvellous Foundation, which is a registered charity.
- Pumping Marvellous Foundation has received 75% pharmaceutical company funding in the past two years, but none from the submitting company. Patients with a history of myocardial infarction (MI) have a risk of having an atherothrombotic event and this awareness may lead to anxiety.

- Patients and their families and carers would welcome more effective therapy options for high risk patients to prevent atherothrombotic events.

- Ticagrelor is an oral formulation which can be easily slotted into a patient's drug regime.

- It is important that patients and their families are fully informed about the potential adverse effects. However, as atherothrombotic events carry a very high risk of either a steep reduction in the quality of life or death, some patients will welcome the option of dual therapy with ticagrelor and aspirin as a protective measure for their future quality of life.

Additional information: guidelines and protocols

SIGN published guidelines for 'Acute Coronary Syndrome; A national clinical guideline' in April 2016 (SIGN 148).[7] It recommends that following acute coronary syndrome, all patients should be maintained on long-term aspirin at a dose of 75mg daily. Patients should receive dual antiplatelet therapy for six months. Longer durations may be used where the risks of atherothrombotic events outweigh the risk of bleeding. Shorter durations may be used where the risks of bleeding outweigh the risk of atherothrombotic events. The guideline notes that decisions for individual patients are complicated by the fact that those factors which predict increased cardiovascular risk also predict bleeding. In terms of anticoagulant therapy, the guideline recommends that patients with acute coronary syndrome should not be offered rivaroxaban, apixaban or dabigatran in addition to dual antiplatelet therapy.

National Institute for Health and Care Excellence (NICE) clinical guideline (CG167) 'myocardial infarction with ST-segment elevation: acute management' published in July 2013 incorporates NICE technology appraisals into the guidance.[8] It recommends aspirin to all people after an MI, including those who have had an MI more than 12 months ago and continue it indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. For patients with aspirin hypersensitivity, clopidogrel monotherapy is suggested as an alternative treatment. The guideline recommends ticagrelor in combination with low-dose aspirin for up to 12 months as a treatment option in adults with acute coronary syndromes. It also recommends clopidogrel as a treatment option for up to 12 months to those who have had an NSTEMI and for at least one month and consider continuing for up to 12 months to those who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent. It is recommended that the second antiplatelet agent is continued for up to 12 months in those who have had a STEMI and who received coronary artery bypass graft surgery.

The European Society of Cardiology published guidelines in 2016 on cardiovascular disease prevention in clinical practice.[9] This recommends that:

- in acute coronary syndromes, a P2Y12 inhibitor for 12 months in addition to aspirin, unless there are contra-indications such as excessive risk of bleeding.
- P2Y12 inhibitor administration for a shorter duration of 3 to 6 months after DES implantation may be considered in patients deemed at high risk of bleeding.
- The use of a P2Y12 inhibitor in addition to aspirin beyond 1 year may be considered after careful assessment of ischaemic and bleeding risks of the patient.
- aspirin for the chronic phase (>12 months) after MI.
- In patients with non-cardioembolic ischaemic stroke or TIA, prevention with aspirin only, or dipyridamole plus aspirin or clopidogrel alone.

- Prasugrel is not recommended in patients with stable CAD.
- Ticagrelor is not recommended in patients with stable CAD without a previous ACS.
- In patients with non-cardioembolic cerebral ischaemic events, anticoagulation is not recommended.
- Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.

Additional information: comparators

Clinical experts consulted by SMC reported that there may be limited off-label use of clopidogrel.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Ticagrelor	**60mg orally twice daily**	**710**
Clopidogrel*	75mg orally once daily	25

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 5 December 2016. *Clopidogrel is not licensed for use for longer than 12 months.

Additional information: budget impact

The submitting company estimated there would be 779 patients eligible for treatment with ticagrelor in year 1 rising to 4,533 patients in year 5. The estimated uptake rate was 3% in year 1 (42 patients), rising to 11% in year 5 (378 patients), with a discontinuation rate of 12% applied in year 1 and 23% in year 5.

The gross impact on the medicines budget was estimated to be £30k in year 1, rising to £269k in year 5. As no medicines were assumed to be displaced, the net medicines budget impact is equivalent to the gross impact.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. AstraZeneca UK Limited. Brilique 60 mg and 90 mg film coated tablets. Summary of Product Characteristics. Last updated 28 September 2016.
2. Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF*, et al.* Design and rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. Am Heart J. 2014;167(4):437-44 e5.
3. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC*, et al.* Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. N Engl J Med. 2015;372(19):1791-800.
4. European Medicines Agency. TICAGRELOR (Brilique) European Public Assessment Report (EPAR) EMEA/H/C/001241/0029/G. 2016.
5. Timmis A RE, Chung SC, Pujades-Rodriguez M, Moayyeri A, Stogiannis D, et al. Prolonged dual antiplatelet therapy in stable coronary disease: comparative observational study of benefits and harms in unselected versus trial populations. BMJ.353(i3163).
6. Timmins A RE, Chung SC et al. Prolonged dual antiplatelet therapy in stable coronary disease: comparative observational study of benefits and harms in unselected versus trial populations. Epub BMJ 2016;353:i3163 | doi: 10.1136/bmj.i3163.
7. Scottish Intercollegiate Guidelines Network. SIGN 148 Acute Coronary Syndrome 2016.
8. National Institute for Health and Care Excellence. Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 172, November 2013. .
9. Piepoli MP, Hoes AW, Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practiceEuropean Heart Journal doi:10.1093/eurheartj/ehw106.

This assessment is based on data submitted by the applicant company up to and including 17 February 2017.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.