

ticagrelor 90mg film-coated tablets (Brilique®)

SMC No. (699/11)

AstraZeneca

08 April 2011

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

ADVICE: following a full submission

ticagrelor film-coated tablets (Brilique®) are accepted for use within NHS Scotland.

Indication under review: co-administered with aspirin, for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (unstable angina, non ST elevation myocardial infarction [NSTEMI] or ST elevation myocardial infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

As dual therapy with aspirin, ticagrelor demonstrated a significant reduction in ischaemic events compared with another antiplatelet drug without significantly increasing the incidence of study-defined major bleeding.

Alternative treatments are available at a lower drug acquisition cost.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Co-administered with aspirin, for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (unstable angina, non ST elevation myocardial infarction [NSTEMI] or ST elevation myocardial infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

Dosing Information

Initiated with a single loading dose of 180mg and continued at a dose of 90mg twice daily. Treatment is recommended for up to 12 months unless discontinuation is clinically indicated. Ticagrelor should be used with a maintenance dose of aspirin of 75 to 150mg daily, unless contra-indicated.

Product availability date

6 January 2011

Summary of evidence on comparative efficacy

Ticagrelor is a new antiplatelet agent acting as a reversible, selective antagonist of the P2Y₁₂ adenosine diphosphate (ADP) receptor thus preventing ADP-mediated platelet activation and aggregation.

One pivotal, phase III study compared ticagrelor with clopidogrel in 18,624 hospitalised patients with onset of symptoms of acute coronary syndrome within 24 hours. Eligible patients had ST elevation myocardial infarction (STEMI) of ≥ 0.1 mV in at least two contiguous leads or new left bundle branch block with intention to carry out primary PCI, or unstable angina or non-ST elevation myocardial infarction (NSTEMI) but with at least two of the following criteria (i) ST-segment changes indicative of ischaemia; (ii) a positive test for a biomarker indicative of myocardial necrosis; or (iii) one of several risk factors (age >60 ; previous myocardial infarction (MI) or coronary artery bypass graft (CABG); coronary artery disease with stenosis $\geq 50\%$ in at least two vessels; previous ischaemic stroke, transient ischaemic attack, carotid stenosis $\geq 50\%$ or previous cerebral revascularisation; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction). Patients were randomised in a ratio of 1:1 using a double-blind, double-dummy design to receive ticagrelor 90mg twice daily after an initial loading dose of 180mg or clopidogrel 75mg daily after an initial loading dose of 300mg in patients who had not received an open-label loading dose of clopidogrel or had not been taking clopidogrel or ticlopidine for at least 5 days before randomisation. In patients undergoing PCI, after randomisation an additional blinded dose of study drug was administered at the time of PCI: either 300mg of clopidogrel, at the discretion of the investigator or, only for those patients undergoing PCI at least 24 hours after randomisation, 90mg of ticagrelor. It was recommended that study drug was withheld in patients undergoing CABG for 24 to 72 hours in the ticagrelor group and 5 days in the clopidogrel group. All patients also received aspirin 75 to 100mg daily (with a preferred loading

dose of 325mg [range 160 to 500mg]) in aspirin-naïve patients), unless intolerant. For patients undergoing stent placement, aspirin up to 325mg daily was permitted for 6 months.

Treatment with study medication was planned for 12 months but if the target of 1,780 primary endpoints had been reached, patients were allowed to leave the study at their 6 or 9 month visit. Glycoprotein IIb/IIIa inhibitors and parenteral anticoagulants were permitted during the study but long-term low-molecular-weight heparins were not recommended. Patients who had received fibrinolytic therapy within the previous 24 hours, or in whom it was planned, were excluded from the study. Oral anticoagulation was not permitted.

The primary endpoint was the time to first occurrence of any event from the composite of death from vascular causes, MI and stroke, with analysis in the intention to treat population. After a median treatment duration of 9.1 months, there was a significantly lower incidence of the primary composite endpoint in the ticagrelor group, as detailed in the table below. This was due to a lower incidence of both death from vascular causes and MI. The incidence of stroke was numerically higher in the ticagrelor group but the difference was not statistically significant.

Table: Results of primary composite endpoint* and its components

Endpoint	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	Hazard ratio (95% CI) for ticagrelor; p-value
Primary composite endpoint			
Death from vascular causes, myocardial infarction or stroke	864 (9.8%)	1014 (11.7%)	0.84 (0.77 to 0.92) p<0.001
Components of primary endpoint			
Death from vascular causes	353 (4.0%)	442 (5.1%)	0.79 (0.69 to 0.91) p=0.001
Myocardial infarction	504 (5.8%)	593 (6.9%)	0.84 (0.75 to 0.95) p=0.005
Stroke	125 (1.5%)	106 (1.3%)	1.17 (0.91 to 1.52) p=0.22

* percentages are Kaplan-Meier estimates of the rate of the endpoint at 12 months.

The beneficial effect of ticagrelor was evident at 30 days (HR: 0.88, p=0.0446), was maintained until the end of the study and was demonstrated in patients with or without ST-segment elevation.

The key secondary endpoint was the primary composite endpoint analysed in the subgroup of patients planned for invasive management, which comprised 72% (13,408/18,624) of the overall population. This endpoint was reported in significantly fewer ticagrelor than clopidogrel patients in this subgroup: 8.9% (569/6732) versus 11% (668/6676) respectively, corresponding to a hazard ratio of 0.84 (95% CI: 0.75 to 0.94), p=0.003. A secondary endpoint of note was death from any cause, reported in 4.5% (399/9333) ticagrelor patients and 5.9% (506/9291) clopidogrel patients, corresponding to a hazard ratio of 0.78 (95% CI: 0.69 to 0.89), p<0.001.

A number of sub-studies assessed the relative effects of ticagrelor and clopidogrel in subgroups of the overall study population, including those managed invasively and medically, those who underwent CABG, those with diabetes and patients with genetic polymorphisms which may affect the response to clopidogrel. The results of these analyses were generally consistent with the primary analysis.

Summary of evidence on comparative safety

There was a higher overall incidence of adverse events in the ticagrelor group (73% [6714/9235]) than in the clopidogrel group (70% [6398/9186]). However, the incidence of serious adverse events was similar in both groups (20.2% and 20.3% respectively).

The key safety issue with an antiplatelet medicine is the risk of bleeding. The pivotal study used its own definition of major bleeding which defined major life-threatening bleeding as: fatal, intracranial, intrapericardial with cardiac tamponade, hypovolaemic shock or severe hypotension requiring pressors or surgery, associated with a decrease in haemoglobin of >5g/dL or requiring transfusion of ≥ 4 units of whole blood or packed red blood cells (PRBC); and major-other bleeding as: significantly disabling (e.g. intraocular with permanent vision loss), associated with a decrease in haemoglobin of 3 to 5g/dL or requiring transfusion of 2 to 3 units of whole blood or PRBC. The key safety endpoints related to bleeding are listed in the table below.

Table: Results of key safety endpoints*

Safety endpoint	Ticagrelor (n=9235)	Clopidogrel (n=9186)	Hazard ratio (95% CI) for ticagrelor	p-value
Major bleeding as defined by: Study	961 (11.6%)	929 (11.2%)	1.04 (0.95 to 1.13)	0.43
TIMI**	657 (7.9%)	638 (7.7%)	1.03 (0.93 to 1.15)	0.57
Life-threatening/fatal bleeding	491 (5.8%)	480 (5.8%)	1.03 (0.90 to 1.16)	0.70
Fatal bleeding	20 (0.3%)	23 (0.3%)	0.87 (0.48 to 1.59)	0.66
Non-intracranial fatal bleeding	9 (0.1%)	21 (0.3%)	NR	0.03
Intracranial bleeding	26 (0.3%)	14 (0.2%)	1.87 (0.98 to 3.58)	0.06
Fatal	11 (0.1%)	1 (0.01%)	NR	0.02
Non-fatal	15 (0.2%)	13 (0.2%)	NR	0.69
Non-CABG related major bleeding defined by study	362 (4.5%)	306 (3.8%)	1.19 (1.02 to 1.38)	0.03
CABG-related major bleeding defined by study	619 (7.4%)	654 (7.9%)	0.95 (0.85 to 1.06)	0.32
Major or minor bleeding defined by study	1339 (16.1%)	1215 (14.6%)	1.11 (1.03 to 1.20)	0.008
Major or minor bleeding defined by TIMI	946 (11.4%)	906 (10.9%)	1.05 (0.96 to 1.15)	0.33

* percentages are Kaplan-Meier estimates of the rate of the endpoint at 12 months.

** TIMI: Thrombolysis in Myocardial Infarction

Although not significantly different, the incidence of study-defined major bleeding was numerically slightly higher in the ticagrelor group. Non-CABG-related study-defined major bleeding and study-defined major or minor bleeding were significantly higher in the ticagrelor group. Intra-cranial bleeding was numerically more common in the ticagrelor than the clopidogrel group and fatal intra-cranial bleeding was significantly more common. However, fatal, non-intra-cranial bleeding was significantly more common in the clopidogrel group.

There was a significantly higher incidence of dyspnoea in ticagrelor patients (14%) than in the clopidogrel group (7.8%). This led to discontinuation in 0.9% and 0.1% of patients respectively.

The SPC reports that 2.2% and 0.6% respectively were considered by the investigator as related to treatment.

In the ticagrelor group compared with the clopidogrel group, there were also significantly greater increases from baseline in uric acid and creatinine levels during the study.

Summary of clinical effectiveness issues

Ticagrelor is a new antiplatelet agent which acts as a reversible, selective antagonist of the P2Y₁₂ ADP receptor. It is a more potent antiplatelet agent than clopidogrel and, unlike clopidogrel and prasugrel, ticagrelor is not a pro-drug. It offers another treatment option allowing antiplatelet therapy to be individualised according to the patient's risk of ischaemia and bleeding.

In the pivotal study, ticagrelor significantly reduced the incidence of ischaemic events compared with clopidogrel as measured by the primary composite endpoint of cardiovascular death, MI and stroke, with an absolute risk reduction of 1.9% and a number needed to treat of 53 with ticagrelor instead of clopidogrel to prevent one primary endpoint. Benefit was evident after 30 days of study drug and continued until the end of the study. The difference between the treatment groups was driven by a difference in the incidence of cardiovascular death and MI and there was no significant difference in the incidence of stroke, which was numerically higher in the ticagrelor group. The pivotal study included patients across the range of acute coronary syndromes and treatment benefit was seen in those patients with or without ST-segment elevation. However, patients who had received fibrinolytic therapy within the previous 24 hours, or in whom it was planned, were excluded from the study. Treatment benefit was also consistent across a range of subgroup analyses, including patients managed invasively or medically, those who underwent CABG or PCI and those with diabetes. Ticagrelor was also associated with a total mortality benefit over clopidogrel. In the pivotal trial a pre-specified, hierarchical test sequence was employed to control for overall type 1 error in all 20 endpoints. Analysis of total mortality favoured ticagrelor but because the prior test in the hierarchy sequence was not found to be significant the result for total mortality should be viewed as a directional finding only.

Although not significantly different, the incidence of study-defined major bleeding was numerically slightly higher and non-CABG related study-defined major bleeding and study-defined major or minor bleeding were significantly higher in the ticagrelor group. Intra-cranial bleeding was numerically more common in the ticagrelor group than in the clopidogrel group and fatal intra-cranial bleeding was significantly more common. However, fatal, non-intra-cranial bleeding was significantly more common in the clopidogrel group. The different definitions of bleeding between the pivotal study and other antiplatelet studies make comparison between studies difficult.

The pivotal study had a number of limitations. Firstly, it did not exclude patients already receiving treatment with clopidogrel and may have included a small proportion of patients who were poor responders to clopidogrel and therefore at higher risk of an ischaemic event. Clopidogrel patients also received different loading doses depending on whether or not they had already been receiving clopidogrel, and at the discretion of the investigator if undergoing PCI. Secondly, study treatment was intended to continue for up to 12 months but patients were allowed to stop after 6 or 9 months if sufficient primary events had been recorded. Patients

therefore received different durations of treatment and the median duration of study treatment was 9.1 months, which is shorter than the 12 months recommended by some current guidelines.

Although the pharmacological effects of ticagrelor are more rapidly reversible than those of the irreversible inhibitors, clopidogrel and prasugrel, the recommended discontinuation time before elective surgery is the same. This reversibility also means that ticagrelor requires twice-daily dosing which may affect adherence compared with once-daily clopidogrel.

Clopidogrel is licensed for other therapeutic indications including use for the prevention of atherothrombotic events in patients suffering from ischaemic stroke or established peripheral arterial disease as well as myocardial infarction. In STEMI patients, clopidogrel is licensed specifically for use in medically treated patients who are eligible for thrombolytic therapy. In contrast, the SPC for ticagrelor recommends caution if used in patients who receive fibrinolytics within 24 hours of ticagrelor dosing. The recommended duration for clopidogrel in NSTEMI patients is for up to 12 months while in STEMI patients is 4 weeks. Prasugrel is licensed for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing primary or delayed PCI with a recommended duration of up to 12 months. These differences are largely due to differences in the evidence-base.

The submission included key data taken from an independent, published indirect comparison which included three studies and a total of 32,893 patients. As highlighted by the submitting company, this comparison had a number of key limitations. However, this publication suggested that ticagrelor and prasugrel appear similarly superior to clopidogrel in terms of efficacy and safety although prasugrel appears to offer more protection from stent thrombosis but also causes more bleeding.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing ticagrelor to clopidogrel in adult patients with acute coronary syndromes. Clopidogrel is the current standard treatment in Scotland and therefore the relevant comparator. A secondary analysis was provided of ticagrelor compared to prasugrel in patients with acute coronary syndromes undergoing primary or delayed PCI. A lifetime horizon was used in both analyses. In each analysis, the duration of treatment with ticagrelor, clopidogrel or prasugrel was assumed to be one year.

The economic model was structured around a decision tree for the initial year of the model and thereafter a Markov model with health states of MI, post-MI, non-fatal stroke, post-stroke, no event and death. Clinical data for the comparison with clopidogrel were taken from the pivotal trial for the decision tree phase of the model and from an indirect comparison, using the Bucher method, for the decision tree phase in the case of the comparison with prasugrel. The manufacturer adjusted the baseline risks from the trial to take account of the older population of acute coronary syndrome patients in Scotland compared to patients in the pivotal study. For the Markov phases of the models, the risks of further events were taken from literature sources and published life tables. No treatment effects were assumed for any of the treatments beyond one year and therefore a key driver of the model was the distribution of patients entering the various states of the Markov model. Adverse events such as bleeding were not specifically accounted for in the model structure but the manufacturer asserted these were incorporated through the utility measurement and resource use aspects of the model.

For the decision tree phase of the model, utility values were estimated directly from EQ-5D data collected from patients in the pivotal trial. For the Markov phase of the model, published values were used. Resource use for the decision tree was estimated from patient-level data collected during the pivotal trial and from literature sources for the Markov states.

For the comparison with clopidogrel, the base case cost per quality adjusted life year (QALY) was £3,966 based on a QALY gain of 0.095 and incremental costs of £375. Most of the gain in QALYs arose from gains in the 'no event' state. For the comparison with prasugrel, the cost per QALY was £3,482 based on a QALY gain of 0.065 and incremental costs of £227. It should be noted that, as is normal practice with economic evaluations, these incremental costs reflect all the costs in the model, and not only the difference in drug acquisition costs between treatments.

Extensive sensitivity analysis was provided for the comparison with clopidogrel. This indicated that the incremental cost effectiveness ratios (ICERs) were sensitive to the following: costs associated with the 'no event' state in the decision tree; the use of common costs for each health state in the decision tree, rather than differentiating by whether a patient was on ticagrelor or clopidogrel; the hazard ratio for all cause mortality; and using shorter time horizons.

The key limitations with the analysis were:

- Resource use for the health states in the decision tree model differed depending on whether a patient was treated with ticagrelor or clopidogrel, based on patient level data. While use of patient-level data is acceptable, the ICER increased to £6,717 per QALY when common costs for each state were used.
- In addition, the event costs for the decision tree were taken from patient level cost data collected as part of the pivotal trial. Some of the resulting health state costs seem relatively high. Sensitivity analysis was subsequently provided which reduced the event costs by 50% and applied common costs in each arm of the model. This increased the ICER to £7,346 per QALY.
- The recommended duration of treatment with clopidogrel in Scotland may be less than the duration used in the model. An additional analysis was provided to approximate treatment with clopidogrel for three months versus treatment with ticagrelor for one year. This increased the cost per QALY to £8,905.

The additional sensitivity analyses provided by the manufacturer addressed the main limitations with the analysis and provided some reassurance that the cost per QALY is still within acceptable limits when more conservative assumptions are used. Therefore, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline 94 “Unstable angina and NSTEMI: “The early management of unstable angina and non-ST-segment elevation myocardial infarction”, in March 2010. The guideline predates the availability of ticagrelor but in terms of antiplatelet therapy recommends: for people at increased risk of mortality and no contraindications or for all patients with no contraindications who may undergo PCI within 24 hours of admission to hospital, clopidogrel in combination with low-dose aspirin for 12 months after the most recent acute episode of non-ST segment elevation acute coronary syndrome. Prasugrel in combination with aspirin is an option for patients undergoing PCI who have diabetes or have had stent thrombosis with clopidogrel.

The Scottish Intercollegiate Guidelines Network (SIGN) published Acute Coronary Syndromes, a national clinical guideline, in February 2007. These guidelines predate the availability of ticagrelor but recommend that patients with an acute coronary syndrome (in the presence of ischaemic ECG changes or elevation of cardiac markers) should be treated immediately with both aspirin (300mg) and clopidogrel (300mg); that clopidogrel should be continued for up to 4 weeks in patients with STEMI and for 3 months in patients with NSTEMI which may need to be extended to six months after drug-eluting stent implantation.

The European Society of Cardiology (ESC) published guidelines on myocardial revascularisation in 2010 which include recommendations on antiplatelet options. In patients undergoing elective PCI, the guideline recommends clopidogrel at a loading dose of 300mg if initiated more than 6 hours before PCI or 600mg if more than 2 hours before. In patients with NSTEMI or STEMI, the guideline recommends clopidogrel (with 600mg loading dose as soon as possible), prasugrel or ticagrelor. Dual antiplatelet therapy after PCI for acute coronary syndromes is recommended for a duration of one year, irrespective of the revascularisation strategy.

The ESC published guidelines for the diagnosis and treatment of non ST elevation acute coronary syndrome in 2007. These guidelines predate the availability of ticagrelor but recommend that all patients receive an immediate 300mg loading dose of clopidogrel followed by 75mg clopidogrel daily for 12 months unless there is an excessive risk of bleeding. In patients considered for an invasive procedure/PCI a loading dose of 600mg of clopidogrel may be used to achieve more rapid inhibition of platelet function.

The ESC published guidelines for the management of STEMI in 2008. These guidelines predate the availability of ticagrelor but recommend an oral loading dose of at least 300mg of clopidogrel preferably 600mg to be administered as soon as possible to all STEMI patients undergoing PCI. A maintenance dose of clopidogrel 75mg daily should be continued for 12 months irrespective of acute treatment.

Additional information: comparators

The key comparator is clopidogrel but prasugrel may also be considered a comparator in the subgroup of patients undergoing primary or delayed PCI who are eligible to receive the 10mg dose of prasugrel.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Ticagrelor	Orally 180mg loading dose then 90mg twice daily	711
Prasugrel	Orally 60mg loading dose then 10mg daily	627
Clopidogrel	Orally 300mg loading dose then 75mg daily	39

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27 January 2011.

Additional information: budget impact

The manufacturer estimated a net gross drug budget impact of £333k in year one rising to £5.1m in year five. After accounting for the additional costs of treating increased dyspnoea in ticagrelor patients, these costs increased to £334k and £5.1m respectively. After taking into account the cost offset from clopidogrel prescribing the net drug budget impact was estimated at £315k in year one rising to £4.8m in year five. The manufacturer also offset savings associated with reduced resource use from hospitalisations, investigations and interventions that may be associated with ticagrelor compared to clopidogrel to give an overall net budget impact of £185k in year one rising to £2.8m in year five. Many of these savings would be resource-releasing rather than cash-releasing savings.

The manufacturer assumed that 15,822 patients would be eligible per year. The manufacturer assumed a market share of 9% in year one rising to 49% by year five to give patient numbers of 1,424 in year one rising to 7,753 in year five. The budget impact calculations reflect assumptions that not all patients would be treated with a full year of ticagrelor due to phased uptake over the course of a year. SMC noted that the manufacturer may have underestimated the potential uptake of this product.

References

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

Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N.Engl.J.Med. 2009;361:1045-57.

James S, Akerblom A, Cannon CP et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am.Heart J. 2009;157:599-605.

Biondi-Zoccai G, Lotrionte M, Agostoni P et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. Int.J.Cardiol. 2010

European Medicines Agency. Assessment report for Brilique EMEA/H/C/1241. www.ema.europa.eu

Schomig A. Ticagrelor – is there a need for a new player in the antiplatelet therapy field? Editorial. N Engl J Med 2009;361:1108-11.

This assessment is based on data submitted by the applicant company up to and including **11 March 2011**.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.