Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Cangrelor for preventing atherothrombotic events in people undergoing percutaneous coronary intervention or surgery

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of cangrelor within its licensed indication for preventing atherothrombotic events in people with coronary heart disease undergoing percutaneous coronary intervention or surgery.

Background

Coronary heart disease (CHD) also known as coronary artery disease or ischaemic heart disease is narrowing (stenosis) of the coronary arteries as a result of deposition of atherosclerotic plaque, which results in an insufficient supply of oxygen to the heart muscle. Coronary artery stenosis may lead to angina or chest pain that may be severe enough to restrict or prevent exertion. Stable angina has a typical pattern and occurs when heart is working harder and needs more oxygen, such as during exercise. A sudden and critical reduction of the blood supply to the heart may result in acute coronary syndrome (ACS). It encompasses a spectrum of disease including acute myocardial infarction (MI) and unstable angina. The presence of ST-segment-elevation (STEMI) on an electrocardiogram usually indicates total occlusion of the affected artery, resulting in necrosis of the tissue supplied by that artery. Non ST-segment-elevation (NSTEMI) differs from unstable angina primarily in the severity of myocardial ischaemia. In NSTEMI, the ischaemia is severe enough to result in the release of biochemical markers of myocardial injury into the blood.

The prevalence of coronary heart disease in England is 6.5% in men and 4.0% in women; however the burden of disease varies between ethnic groups. There were around 23,700 deaths due to acute myocardial infraction in 2011 in England and Wales.

Coronary revascularisation (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) is recommended for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment (NICE Clinical guideline 126) as well as for patients with NSTEMI who have an intermediate or higher risk of adverse cardiovascular events (NICE Clinical Guideline 94). For STEMI, NICE clinical guideline 167 recommends immediate coronary reperfusion therapy preferably with primary PCI. It also recommends PCI in patients with STEMI who are initially treated with fibrinolysis but show signs of failed coronary reperfusion or have recurrent myocardial ischaemia. Stents are used routinely in patients undergoing PCI to maintain patency of the diseased artery and to prevent

restenosis. Patients undergoing PCI are treated with a loading dose of an oral P2Y12 receptor inhibitor (such as clopidogrel, prasugrel or ticagrelor) to prevent atherothrombotic events. Following PCI most patients receive long term dual antiplatelet therapy with aspirin and an oral P2Y12 receptor inhibitor to prevent stent thrombosis. Patients receiving antiplatelet therapy are exposed to an excessive risk of bleeding. Elective surgeries should be avoided while patients are on antiplatelet therapy. For more urgent interventions such as CABG or PCI, discontinuation of antiplatelet therapy for a time period before surgery, that allows recovery of platelet function is often necessary. In that scenario the higher risk of athrothrombotic events associated with interruption of antiplatelet therapy must be balanced with the risk of bleeding. In patients with low risk of adverse cardiovascular events, CG94 recommends discontinuing clopidogrel 5 days before CABG. While for patients at intermediate or higher risk, it recommends that decision on continuation of clopidogrel should to be based on the balance between ischaemic and bleeding risks. In clinical practice, 'bridging therapy' with short-acting agents (such as glycoprotein IIb/IIIa inhibitors [eptifibatide or tirofiban] and/or heparin) may be used before surgery or interventional procedures associated with the risk of bleeding.

The technology

Cangrelor (brand name unknown, The Medicines Company) is a non-thienopyridine, adenosine triphosphate analogue that binds to the P2Y12 class of adenosine diphosphate receptors on platelets and inhibits platelet activation and aggregation. It is characterised by reversible platelet inhibition with a quick onset and short duration of effect. Cangrelor is administered intravenously.

Cangrelor does not currently have a UK marketing authorisation for preventing atherothrombotic events in people undergoing percutaneous coronary intervention or surgery. It has been studied in clinical trials compared with clopidogrel in adults with coronary heart disease undergoing percutaneous coronary intervention. It has also been studied in clinical trials compared with placebo as an anti-platelet bridging therapy in adults undergoing CABG surgery who had received a thienopyridine (ticlopidine, clopidogrel, prasugrel).

Intervention(s)	Cangrelor
Population(s)	• People with coronary heart disease undergoing percutaneous coronary intervention • People on oral P2Y12 inhibitor therapy undergoing surgery

Comparators	For people undergoing percutaneous coronary intervention • Clopidogrel • Prasugrel • Ticagrelor For people on anti-platelet therapy undergoing surgery • Discontinuation of all anti-platelet therapy • Bridging treatment with glycoprotein IIb/IIIa inhibitors and/or heparin • Continuation of existing anti-platelet therapy
Outcomes	The outcome measures to be considered include: • non-fatal and fatal cardiovascular events • mortality (from any cause) • atherothrombotic events • incidence of revascularisation procedures • bleeding events • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 236, Oct 2011, 'Ticagrelor for the treatment of acute coronary syndromes'. Transferred to the 'static guidance list' in April 2013. Technology Appraisal No. 230, Jul 2011, 'Bivalirudin for the treatment of ST-segment-elevation myocardial infarction'. Transferred to the 'static guidance list' in

	August 2012. Technology Appraisal No. 182, Oct 2009, 'Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention'. Currently being reviewed. Earliest anticipated date of publication August 2014. Technology Appraisal No. 80, Jul 2004, 'Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome'. Transferred to the 'static guidance list' in March 2013. Technology Appraisal in Preparation, 'Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182)'. Earliest anticipated date of publication August 2014. Technology Appraisal in Preparation, 'Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome'. Earliest anticipated date of publication March 2015 Related Guidelines: Clinical Guideline No. 167, Jul 2013, 'Myocardial infarction with ST-segment elevation: The acute management of myocardial infarction with ST-segment elevation'. Review Proposal Date: TBC. Clinical Guideline No. 126, Jul 2011, 'Management of stable angina'. Review Proposal Date: July 2014. Clinical Guideline No. 95, Mar 2010 'Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin'. Review Proposal Date: March 2013. Clinical Guideline No. 94, Mar 2010 'Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction' Review Proposal Date: March 2013. Clinical Guideline No. 48, May 2007 'Secondary prevention in primary and secondary care for patients following a myocardial infarction'. Currently under review. Earliest anticipated publication date Nov 2013. Clinical Guideline in Preparation, 'Post myocardial infarction Secondary prevention in primary and secondary care for patients following a myocardial infarction (partial update of Partial update of NICE CG48)'. Earliest anticipated publication date Nov 2013.

	Related Interventional Procedures: Interventional Procedure Guidance No. 377, Jan 2011, 'Off-pump coronary artery bypass grafting'. Related Quality Standards: Quality Standard in preparation, 'Acute coronary syndromes (including myocardial infarction)'. Earliest anticipated date of publication: TBC http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways: NICE Pathway: Myocardial infarction with ST-segment elevation, Pathway created: July 2013, http://pathways.nice.org.uk/pathways/myocardial-infarction-with-st-segment-elevation NICE Pathway: Acute coronary syndrome, Pathway created: July 2013, http://pathways.nice.org.uk/pathways/acute-coronary-syndrome NICE Pathway: Stable angina, Pathway created: July 2013, http://pathways.nice.org.uk/pathways/stable-angina
Related NHS England Policy	National service framework: coronary heart disease, March 2000, Department of Health: https://www.gov.uk/government/publications/quality-standards-for-coronary-heart-disease-care Primary percutaneous coronary intervention (PPCI) services for ST-elevated myocardial infarction, Manual for prescribed specialised services, November 2012, NHS Commissioning Board:http://www.england.nhs.uk/wp-content/uploads/2012/12/pss-manual.pdf

Questions for consultation

Have all relevant comparators for cangrelor been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for prevention of atherothrombotic events in people undergoing percutaneous coronary intervention?

- Which treatments are considered to be established clinical practice in the NHS for bridging antiplatelet therapy in people with coronary stents undergoing surgery?

Is an appraisal of cangrelor as a bridging therapy likely to be of value to the NHS?

Is cangrelor likely to be administered as monotherapy or in combination with aspirin in clinical practice?

Are there any subgroups of people in whom cangrelor is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider cangrelor will fit into the existing NICE pathways, Stable angina, Acute coronary syndrome and Myocardial infarction with ST-segment elevation?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which cangrelor will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider cangrelor to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of cangrelor can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. Should the two different indications of cangrelor

(prior to PCI and as a bridging therapy) be appraised in two separate single technology appraisals?

We welcome comments on the appropriateness of appraising this topic through the single technology appraisal process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)

Subject to referral by the Department of Health, the invite for participation in this technology appraisal is anticipated for after January 2014, when new arrangements for the pricing of pharmaceuticals are expected to be in place. Consequences for this appraisal will be explored through further consultation on the scope pre-invitation.