Bayer HealthCare

Response to the NICE Appraisal Consultation Document (ACD)

Rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome

November 2014

This document sets out Bayer's response to the ACD concerning rivaroxaban for preventing adverse outcomes after acute management of acute coronary syndrome.

Draft recommendation

Bayer is pleased with the draft recommendations and agrees that points 1.2 and 1.3 support the most appropriate use of rivaroxaban in this indication:

1.2 Clinicians should carefully assess the person's risk of bleeding before treatment with rivaroxaban is started. The decision to start treatment should be made after an informed discussion between the clinician and the patient about the benefits and risks of rivaroxaban in combination with aspirin plus clopidogrel or with aspirin alone, compared with aspirin plus clopidogrel or aspirin alone.

1.3 Clinicians should reassess the relative benefits and risks of continuing treatment with rivaroxaban, no later than 12 months after starting treatment.

Indeed, Bayer is committed to introducing rivaroxaban 2.5mg as a responsible partner to the NHS, with a focus on the patients with the highest CV risk and lowest risk of bleeding (in line with the European licence). Rivaroxaban 2.5mg will be commercially available in the UK from Friday, 24th October 2014.

Unmet need

Bayer is pleased that there is recognition of the remaining *high unmet need* despite current management. Notwithstanding the widespread use of antiplatelet agents in the acute and chronic setting, the incidence of CV events such as CV death or MI in the post-ACS population remains high.

Patients who receive recommended dual antiplatelet therapies still have a 10% residual risk of experiencing a major CV event during the 12–15 months after ACS has occurred(1-3).

A study in England found that at 7 years, the risk of all-cause mortality in male and female survivors of first acute myocardial infarction was about twice the risk of all-cause mortality in the general population. By 7 years, the risk of all-cause mortality in both male and female survivors of recurrent AMI was about 3 times higher than the risk of dying in the general population(4).

Innovative approach

Bayer is also pleased to note that the clinical experts advising the appraisal committee observed that due of its different mechanism of action, rivaroxaban could be a useful additional treatment option for some patients receiving clopidogrel plus aspirin or aspirin alone.

The central role of thrombosis in the pathophysiology of ACS, and the platelet-rich composition of arterial thrombi, provide a rationale for the use of antiplatelet agents. After

the rupture or erosion of an atherosclerotic plaque, platelets are recruited to the plaque where they adhere to the vessel wall and recruit further platelets, leading to rapid growth of the thrombus.

After atherosclerotic plaque rupture in patients with ACS, the presence of tissue factor in atherosclerotic plaques and in the blood (following endothelial damage), alongside activated platelets, triggers the coagulation cascade, leading to the generation of thrombin and the conversion of fibrinogen to fibrin, which stabilizes the ACS clot(5-10). In parallel, thrombin stimulates platelets by binding to protease-activated receptor 1 (PAR1; also known as the thrombin receptor), inducing release of adenosine diphosphate and thromboxane A2, which further stimulates platelet activation and aggregation(11;12). Most thrombin is produced on the platelet surface, and binding of thrombin to platelets via glycoprotein Ibα is believed to contribute to platelet activation(13). Because of these various interactions, mechanisms of platelet activation and coagulation are highly interdependent, with thrombin playing a central role in both.

Anticoagulants are an important component of therapy for ACS in the acute setting. However, excess thrombin generation has been found to persist in stable patients for at least 6–12 months beyond the acute presentation of ACS(14;15), providing a rationale for long-term oral anticoagulant therapy for the prevention of recurrent events. The use of anticoagulant therapy in combination with antiplatelet therapy targets complementary mechanisms associated with thrombus formation in patients with ACS.

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.

Rivaroxaban is a significant advance in the secondary prevention of ACS in patients with elevated biomarkers. The *dual pathway treatment strategy*, which recognises the importance of thrombin generation following ACS events and the role that rivaroxaban can play in this, on top of dual antiplatelet therapy offers an *innovative approach* to prevent atherothrombotic events and provides significant mortality benefit.

Of note *rivaroxaban is the only novel OAC with this indication.*

Mortality Benefit and safety

Bayer is pleased to note that the Committee recognised the positive risk benefit profile of rivaroxaban for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

The ATLAS ACS 2 TIMI 51 trial(16) demonstrated that the theoretical benefit of adding an oral anticoagulant (rivaroxaban) to the treatment pathway is translated into improved clinical outcomes.

The 2.5mg rivaroxaban dose was superior to placebo for the primary efficacy endpoint (Composite of death from CV causes, myocardial infarction, and stroke): 6.2% vs. 7.9%; HR=0.80; 95% CI 0.68-0.94; p=0.007)

The event rate for the individual component of CV death was 1.7% in the rivaroxaban 2.5 mg bd group compared to 3.1% in the placebo group with a HR for CV death of 0.55 (95% CI 0.41-0.74) and a p-value of <0.001.

The overall incidence of treatment-emergent non-CABG TIMI major bleeding events, the principal safety outcome, was low. Rivaroxaban 2.5mg twice daily as compared with placebo increased the rates of non-CABG TIMI major bleeding (1.3% vs 0.4%; HR 3.44; 95% CI 1.97-6.01 p<0.001) without an increase in fatal bleeding (0.1% vs 0.2%; HR 0.38 95% CI 0.1-1.45; p=NS).

On balance, the increase in bleeding risk is outweighed by the substantial reduction in risk of death, particularly CV death, from which patients are at high risk after diagnosis of ACS. The benefit risk was further improved in the licensed population (compared to the overall trial population) because of the increased numbers of ischaemic events prevented.

Cost-effectiveness

Bayer is pleased to note that despite difference in opinion in the modelling methodology, the ICERs presented by both Bayer and the ERG were all lower than £10,000 per QALY gained. This led the appraisal committee to conclude that *'Rivaroxaban can be considered a cost-effective use of NHS resources.'*

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