Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of TA182)

Prepared by Daiichi-Sankyo/ Eli Lilly and Company Limited

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Executive Summary

- Prasugrel was shown to be consistently effective across a broad spectrum of ACS-PCI patients in TRITON TIMI 38, the pivotal registration Phase III trial.
- Prasugrel is cost effective compared with generic clopidogrel across all ACS-PCI patients, including those with STEMI, diabetes and UA/NSTEMI at a cost per QALY threshold of £20-30,000.
- Current NICE recommendations for prasugrel are for the high risk patient groups of STEMI, diabetes and patients in whom stent thrombosis has occurred during clopidogrel treatment.
- The strength of the evidence supporting the NICE recommendations for STEMI and patients with diabetes remain, and there is emerging new evidence defining the risk of stent thrombosis, allowing identification of a high risk patient at the point of treatment choice.
- The areas of uncertainty identified during the previous appraisal (inclusion of non-clinical MI, risk factors for stent thrombosis, timing and loading dose of clopidogrel) have been addressed in our submission through additional analyses and additional research, thereby aiding to reduce that uncertainty.
- Potent oral antiplatelets (ticagrelor and prasugrel) are well established for use in STEMI patients, and clinical practice for UA/NSTEMI patients is changing such that potent oral antiplatelets are being considered in high risk NSTEMI patients, identified through risk scoring and clinical judgement.
- Prasugrel, a potent oral antiplatelet, offers a clinically and cost effective treatment option for ACS-PCI patients and presents a suitable treatment option for patients deemed to be at high risk of future ischaemic events.
- It is important to maintain availability and choice of multiple treatment options, when treating high risk complex cardiovascular patients, particularly where there are differences in drug profiles, label indications and precautions/contraindications, as in this case, prasugrel offers value across high risk PCI patients, both STEMI patients, those with diabetes and in addition NSTEMI patients deemed at high risk of future ischaemic events.

Acute coronary syndrome – a diverse population of patients with varying levels of risk

Acute Coronary Syndromes (ACS) are life threatening conditions comprising of clinical symptoms associated with acute myocardial ischemia with or without infarction (Taylor 2007).

The presence of acute chest pain and persistent ST-segment-elevation indicates total occlusion of an affected coronary artery. Most of these patients will ultimately develop an ST-elevation MI (STEMI) resulting in necrosis of the tissue supplied by that artery (Steg, 2012; National Clinical Guideline Centre, 2013). ACS with prolonged pain without ST-segment-elevation is classified as either unstable angina (UA) or non-ST-segment-elevation myocardial infarction (NSTEMI) (Hamm, 2011). Together, these are often referred to as UA/NSTEMI or NSTEACS.

STEMI patients are considered to be high risk patients with urgency for reperfusion (Steg, 2012). In contrast, the population of UA/NSTEMI patients are very heterogeneous with regard to level of risk, which impacts treatment pathway, such that lower risk patients are managed medically and patients with intermediate to high risk features are managed invasively. Percutaneous coronary intervention (PCI) with coronary stenting is endorsed as an early invasive treatment for patients with acute coronary syndrome with intermediate to high risk features (National Clinical Guideline Centre 2010; National Clinical Guideline Centre 2013; Hamm 2011; Steg 2012).

Patients with diabetes mellitus are a subgroup of ACS-PCI patients considered to be a high risk group - presence of diabetes has been identified as an independent predictor of mortality (Hamm 2011).

Stent thrombosis is very serious event associated with a 21-45% mortality rate (Popma et al. 2007, Wiviott et al. 2008b). Recent research conducted by Lilly/Daiichi-Sankyo in response to a research recommendation provided by NICE in TA182, has identified risk factors associated with stent thrombosis, and has developed a risk score enabling early identification of patients at high risk of stent thrombosis.

Historically, clopidogrel plus aspirin was the standard of care for all ACS-PCI patients, irrespective of level or risk. During the last 4 years, two additional options have become available and recommended by NICE – prasugrel and ticagrelor.

Prasugrel has been recommended by NICE in ACS patients undergoing PCI for people with:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary or
- stent thrombosis has occurred during clopidogrel treatment or
- the patient has diabetes mellitus.

Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes (ACS) that is, people:

- with ST-segment-elevation myocardial infarction (STEMI) – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary percutaneous coronary intervention (PCI) **or**

- with non-ST-segment-elevation myocardial infarction (NSTEMI) **or**
- admitted to hospital with unstable angina – defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the characteristics defined in section 1.2. Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.

This choice of oral antiplatelets has led to a shift in clinical practice enabling clinicians to take a more tailored approach to treatment of patients considering the patients risk profile (of both ischaemic events and bleeding events). The potent oral antiplatelets are well established in the STEMI patient group, a clearly defined high risk patient group, which have been recognised to have a need for potent antithrombotic and antiplatelet agents (Steg, 2012). The potent oral antiplatelet ticagrelor is also being considered for use in NSTEMI patients assessed to be at high risk of ischaemic events. However, due to various contraindications and warnings, ticagrelor is not suitable for all patients. Hence, it is important to have treatment choice for when the clinician deems a potent oral antiplatelet to be the optimal treatment.

The technology

Prasugrel (Efient®) is a thienoprydine antiplatelet agent that was launched in early 2009. Prasugrel, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e., unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

Prasugrel should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day. Patients taking prasugrel should also take aspirin daily (75 mg to 325 mg). A treatment of up to 12 months is recommended unless the discontinuation of prasugrel is clinically indicated. A reduction of the maintenance dose to 5mg in patients <60kg (and in patients ≥ 75 years if treatment deemed necessary following careful individual benefit/risk evaluation by prescribing physician) is recommended in the SPC. The use of prasugrel in patients ≥ 75 years of age is generally not recommended.

Prasugrel is available as 5mg and 10 mg film-coated tablets in packs of 28. The list price of prasugrel for both the 5mg dose and 10mg tablets is £47.56 per pack of 28.

The comparators identified are clopidogrel in combination with aspirin and ticagrelor in combination with aspirin. The list price of clopidogrel for 75 mg tablets is £1.83 per pack of 28. The list price of ticagrelor for 90mg tablets is £54.60 per pack of 56 (bi-daily dosing).

Key clinical evidence

The evidence base for prasugrel is primarily provided by TRITON-TIMI 38, which is a large well designed double blind head to head clinical trial in 13,608 patients which compared prasugrel plus aspirin with the standard care antiplatelet therapy, clopidogrel (at the licensed dose) plus aspirin, across a full spectrum of patients with ACS undergoing PCI (UA/NSTEMI and STEMI) (including 73 patients from the UK). The intended study follow up period was 15 months to ensure a median of at least 12 months in line with NICE/ESC recommendations for the duration of clopidogrel therapy. The key study endpoints were ischaemic events for efficacy, and bleeding events for safety. The evidence base is therefore highly relevant to the decision problem.

<u>Efficacy results</u>: Patients in the overall cohort (UA/NSTEMI and STEMI) who received prasugrel (60 mg loading dose, followed by a maintenance dose of 10 mg/day) experienced a large and significant reduction in the primary endpoint (composite of CV death/MI/stroke) as well as in a number of secondary endpoints (including stent thrombosis) compared with patients receiving clopidogrel at the standard approved dose (300 mg loading dose, followed by a maintenance dose of 75 mg/day).

The primary efficacy end point occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel at 15 months (hazard ratio for prasugrel vs. clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; P<0.001) (Wiviott 2007).

Prasugrel demonstrated clinical benefits across the entire spectrum of patients with ACS. In the three groups of UA/NSTEMI, STEMI and patients with diabetes, the incidence of the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke was statistically significantly lower in patients treated with prasugrel compared to clopidogrel:

- **UA/NSTEMI:** Prasugrel 9.9% vs clopidogrel 12.1%; HR = 0.82; 95% CI, 0.73 to 0.93; *p* = 0.002.
- **STEMI:** Prasugrel 10.0% vs clopidogrel 12.4%; HR = 0.79; 95% CI, 0.65 to 0.97; *P* = 0.02.
- **Patients with diabetes mellitus:** Prasugrel 12.2% vs clopidogrel 17.0%; HR = 0.70; 95% CI 0.58 to 0.85; p<0.001

<u>Safety results</u>: Although prasugrel was associated with higher rates of bleeding relative to clopidogrel, it had a favourable benefit-risk profile in the overall study population. Furthermore, in the core clinical cohort (patients without prior TIA/stroke, >60kg and ≤75 years of age), there was a clear efficacy benefit without a statistically significant increase in TIMI-major bleeding.

There was a statistically significant increase in the rate of TIMI non-CABG major bleeding observed with prasugrel compared with clopidogrel (prasugrel 2.4% vs. clopidogrel 1.8% HR 1.32; 95% CI, 1.03 to 1.68; P = 0.03) (Wiviott 2007).

<u>Net Clinical Benefit:</u> The net clinical benefit (as measured by the composite endpoint of death from any cause, non-fatal myocardial infarction, non-fatal stroke, and non-CABG related non-fatal TIMI major bleed) was in favour of prasugrel in the overall trial population (prasugrel 12.2% vs clopidogrel 13.9%; HR, 0.87; 95% CI, 0.79 to 0.95; P = 0.004) (Wiviott 2007).

Additional analyses identified the very elderly (≥ 75 years), patients with low body weight (< 60 kg) or those with prior history of TIA/stroke to be at higher risk of bleeding with the 10 mg maintenance dose, compared with the overall trial population. This has led to the warnings and contraindications described in the SPC.

For those aged < 75 years, body weight ≥ 60 kg, and no history of stroke or transient ischaemic attack (around 80% of the TRITON-TIMI 38 study population), prasugrel demonstrated statistically significant superior efficacy (as measured by the primary composite endpoint) with numerically higher but not statistically significant difference in the rate of non-CABG related TIMI major bleed compared to clopidogrel. A significant net clinical benefit was observed with prasugrel compared with clopidogrel (10.2% vs 12.5%, HR for prasugrel, 0.80; 95% CI, 0.71 to 0.89; P < 0.001) (Wiviott et al., 2007). This is the cohort of patients who are indicated to receive the 10mg maintenance dose in the SPC.

Discussion of previous appraisal

The current recommendations given during the first appraisal for prasugrel in 2009 were based on the strength of the data in the STEMI and diabetic subgroups from TRITON-TIMI 38, and from the substantial benefits seen with prasugrel in the reduction of stent thrombosis.

Key points of discussion during the first appraisal of prasugrel included interpretation of the definition of myocardial infarction, defining the risk factors for stent thrombosis (recommendation for further research), and the size and timing of the clopidogrel loading dose.

New evidence and analyses since the first appraisal, address the uncertainty that was felt, presenting opportunities for wider use of prasugrel.

- The MIs identified in TRITON-TIMI 38 were reanalysed showing that spontaneous and clinical MIs were significantly reduced in prasugrel patients compared with clopidogrel patients. Hence the results are clinically applicable to patients in the UK (see section 5.2.3.2).
- As stent thrombosis is an event associated with a 21-45% mortality rate (Popma et al. 2007, Wiviott et al. 2008b), one could argue that waiting for stent thrombosis to occur would be too late. Further research instigated by Lilly/Daiichi Sankyo as result of the recommendations of the first appraisal has identified risk factors for stent thrombosis which have been validated using individual patient data from TRITON-TIMI 38. (See section 5.6.2). Hence a logical treatment strategy may be the identification of a patient at high risk if stent thrombosis and tailoring therapy accordingly.
- A large trial comparing higher doses of clopidogrel with the licensed dose of clopidogrel in ACS patients failed to meet its primary endpoint, suggesting that the benefits of up-titrating the clopidogrel loading dose are not proven (see section 5.6.3). Furthermore, with regard to timing of the loading dose, additional analyses of TRITON-TIMI 38 data indicated that the timing of the loading dose of clopidogrel did not substantially influence the efficacy of prasugrel (see section 5.6.4).

Key differences in the pivotal trials of prasugrel and ticagrelor mean that a formal indirect comparison is highly problematic and potentially inappropriate

No head to head clinical studies comparing prasugrel and ticagrelor were identified. A formal indirect comparison between prasugrel and ticagrelor was considered, however there are important differences with regard to the population and treatment protocols in the two key trials available to inform an indirect comparison (TRITON-TIMI 38 for prasugrel (Wiviott *et al.* 2007) and PLATlet Inhibition and patient Outcomes (PLATO) for ticagrelor (Wallentin *et al.* 2009)). An indirect comparison between prasugrel and ticagrelor has previously been considered by NICE and by the Liverpool Reviews and Implementation Group (LRiG) and it was concluded that an indirect comparison was inappropriate and would not be credible. The NICE appraisal committee concluded that “no separate recommendations could be made for ticagrelor compared with prasugrel”. Indirect comparisons have been attempted and published by independent researchers using different methodologies. However, no clear benefit of one treatment over the other has been demonstrated and due to the key differences between the trials, the results are inconclusive.

Real World use of prasugrel

Prasugrel is a well-established treatment with over 4 years of experience in clinical practice. Prasugrel has been monitored by EU Regulators in registries and observational studies of more than 26,000 patients across Europe, providing continued evidence of the favourable risk/benefit profile when prasugrel is used in a real-life setting.

Descriptive statistics on the patterns of usage in the UK suggest that prasugrel is being used in line with the licence with the majority of use being in patients less than 75 years of age and greater than 60kg. Of particular note is the high proportion of prasugrel patients who had suffered from a previous MI. As previous MI is a risk factor for future ischaemic events, this suggests that prasugrel is being used in a high risk population.

Economic evaluation – prasugrel presents a cost effective treatment option compared with generic clopidogrel

For consistency, the model that was accepted by NICE for the first appraisal of prasugrel in 2009 is used to evaluate the cost effectiveness of prasugrel compared with generic clopidogrel. Using individual patient data from TRITON-TIMI 38 and thus capturing the heterogeneity across the ACS-PCI population, prasugrel was shown to be cost effective compared with generic clopidogrel over the 40 year time horizon. Specifically, the high risk groups of STEMI and patients with diabetes had highly favourable cost-effectiveness profiles. In the UA/NSTEMI subgroup, which consisted of a heterogeneous population of intermediate and high risk patients, an ICER well below a £20-30,000/QALY threshold was observed.

While the cost of clopidogrel has been significantly reduced since the first appraisal, prasugrel is still a cost-effective option at a cost/QALY of £20-£30,000. This is because the key driver in the model (which is a lifetime model in line with the NICE reference case) is not the cost of the oral antiplatelet treatment but rather the effect on cardiovascular events and the consequent impact on mortality. This is reflected in the extrapolation of the short term data over the long term. This was also an observation made by NICE when considering the review of prasugrel in 2010.

The base-case cost effectiveness results of the various subgroups are presented below.

Table 1: Cost-effectiveness evaluated for the core clinical cohort (excluding prior stroke/TIA and patients <60kg or ≥75 years)

	Clopidogrel	Prasugrel
Total costs	£5,867	£6,463
LYG	14.14	14.20
QALYs	10.97	11.02
Differences in cost		£596
LYG difference		0.07
QALY difference		0.05
Incremental cost per LYG		**£8,979**
Incremental cost per QALY		**£11,796**

Table 2: Cost-effectiveness evaluated for the UA/NSTEMI licensed population (excluding prior stroke/TIA)

	Clopidogrel	Prasugrel
Total costs	£5,480	£6,067
LYG	13.16	13.21
QALYs	10.16	10.20
Differences in cost		£587
LYG difference		0.05
QALY difference		0.04
Incremental cost per LYG		**£11,661**
Incremental cost per QALY		**£15,452**

Table 3: Cost-effectiveness evaluated for the STEMI licensed population (excluding prior stroke/TIA)

	Clopidogrel	Prasugrel
Total costs	£5,437	£6,046
LYG	13.09	13.20
QALYs	10.16	10.25
Differences in cost		£609
LYG difference		0.11
QALY difference		0.09
Incremental cost per LYG		**£5,337**
Incremental cost per QALY		**£6,987**

Table 4: Cost-effectiveness evaluated for the ACS diabetes licensed population (excluding prior stroke/TIA)

	Clopidogrel	Prasugrel
Total costs	£5,209	£5,809
LYG	12.35	12.52
QALYs	9.50	9.63
Differences in cost		£600
LYG difference		0.17
QALY difference		0.13
Incremental cost per LYG		**£3,550**
Incremental cost per QALY		**£4,675**

Conclusion

In 2009 prasugrel was recommended by NICE as a clinically and cost effective treatment option for patients in the NHS for patients with STEMI, diabetes and stent thrombosis. Since that recommendation, prasugrel has become a well-established treatment option in the UK, with 4 years clinical experience. During this time, the availability of generic clopidogrel has consequently reduced the price of clopidogrel. Analysis of the cost effectiveness compared with generic clopidogrel has shown that prasugrel offers a cost effective treatment option across the broad range of ACS-PCI patients, and within the subgroups of the core clinical cohort, STEMI, UA/NSTEMI and patients with diabetes.

The current recommendations for prasugrel are within the high risk groups of patients with STEMI, diabetes mellitus and in patients who have suffered from stent thrombosis receiving clopidogrel. The strength of the data supporting these recommendations remains, and the results of new research can aid in the identification of a patient at high risk of stent thrombosis. The challenges raised by the ERG on the economics have also been addressed with new evidence and research since the last appraisal. The potent oral antiplatelets such as prasugrel are well established in STEMI patients. Furthermore, with the availability of treatment choice in oral antiplatelets, there has been a shift in clinical practice such that the potent antiplatelets are also being considered in other high risk groups (e.g. ticagrelor is being considered in other high risk patient groups, such as high risk NSTEMI, prasugrel for NSTEMI for the high risk group of diabetic patients).

It is important to maintain availability and choice of multiple treatment options, when treating high risk complex cardiovascular patients, particularly where there are differences in drug profiles, label indications and precautions/contraindications, as in this case, prasugrel offers value across high risk PCI patients, both STEMI patients, those with diabetes and in addition NSTEMI patients deemed at high risk of future ischaemic events.