

## Drug Report - prasugrel

### Drug Summary

**Generic Name** prasugrel

**Brand Name** Efient

**Code Name** CS-747; LY-640315

**Synonym/Other**

**Mechanism of Action** platelet aggregation inhibitor; platelet adenosine diphosphate (ADP) receptor antagonist

**Therapy Area** acute coronary syndrome; coronary artery bypass surgery; coronary artery surgery; unstable angina pectoris

**Drug Class** Platelet inhibitors

**Product Type** Drug

**Drug Device**

**Originator** Sankyo Co., Ltd.

**General Comments** Prasugrel is a member of the thienopyridine class of irreversible inhibitors of the adenosine diphosphate (ADP) receptor on platelet cell membranes (P2Y12). The blockade of P2Y12 inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway.

**Licensing Overview** Collaboration agreement between Eli Lilly and Sankyo (now Daiichi Sankyo). Companies have co-development and co-marketing rights in the US and Europe. Sankyo discovered the drug with Ube Industries (Daiichi SEC 6-K, 5/2006).

### Development Status

#### Indication

Treatment of acute coronary syndrome in patients undergoing percutaneous coronary intervention (PCI)

#### Status Comment

Sub-group analysis of TRITON-TIMI 38 study showed that prasugrel reduced risk of heart attack and stent thrombosis compared with clopidogrel. Results of Phase III TRITON-TIMI 38 study showed that prasugrel taken with aspirin reduced risk of combined endpoint of cardiovascular death, non-fatal heart attacks or non-fatal stroke by 19% more than clopidogrel taken with aspirin (Lilly pr, 8/2008). FDA extended review period for NDA based on supplemental information provided during review period. This three month extension allows the FDA time to complete its review (Eli Lilly pr, 6/2008). Results from completed Phase III TRITON-TIMI 38 trial reported: prasugrel plus aspirin produced marked and highly statistically significant reduction in risk of coronary stent thrombosis (ST) as compared to standard therapy with clopidogrel plus aspirin (Daiichi Sankyo pr, 3/2008). MAA submitted. The FDA accepted and designated priority review (Daiichi Sankyo pr, 2/2008). Companies anticipate submission in Europe Q1:2008. NDA was submitted (Daiichi Sankyo pr, 1/2008). Companies anticipate NDA filing at the end of Dec 2007 with launch in 2009, and MAA filing 2008. The FDA would ask for another trial before approval.

Results from Phase III studies showed that prasugrel proved better able to prevent heart problems than Plavix (clopidogrel) but caused a higher risk of serious bleeding (Daiichi Sankyo pr, 12/2007). Phase III TRITON-TIMI 38 trial initiated Nov 2004 in the US in patients who need, or are expected to need, percutaneous coronary intervention, completed. Primary endpoint (composite incidence of cardiovascular death, non-fatal heart attack and non-fatal stroke during a median period of at least 12 months following PCI, as compared vs. clopidogrel) and key secondary endpoint (ST) were met. Additional secondary endpoints were: rehospitalization for a cardiac ischemic event, the need for additional procedures to restore blood flow, non-CABG major, life threatening and minor bleeding, overall safety and tolerability. Study also showed that treatment with prasugrel significantly reduced the relative risk of cardiovascular death, non-fatal heart attack and non-fatal stroke in patients with ST-elevation myocardial infarction (STEMI). Risk of bleeding was not different between prasugrel and clopidogrel treated patients (Daiichi Sankyo pr, 11/2007). Three Phase II trials: PRINCIPLE trial initiated Aug 2006 in the US, France, Germany and Israel in patients who need percutaneous coronary intervention; trial initiated Jul 2006 in the US in subjects who have been taking clopidogrel 75 mg daily following percutaneous coronary intervention (PCI) with placement of a stent, performed to treat acute coronary syndrome (ACS); and trial initiated Mar 2007 in France in patients receiving 10-mg maintenance dose of prasugrel compared with a 150-mg maintenance dose of clopidogrel, following a 900-mg loading dose of clopidogrel. Primary endpoint: pharmacodynamic effect; secondary endpoints: safety and tolerability, pharmacodynamic effects on residual aggregation, monitoring of platelet aggregation. Phase II trial initiated Apr 2003 in the US and Canada in patients undergoing percutaneous coronary intervention, completed (clintrial.gov, as of 7/2007). Phase I comparative trial with clopidogrel in Japan, met positive preliminary results (Daiichi Sankyo Ann Rep, 2006). Three Phase I studies: with a 60 mg loading dose of prasugrel compared vs. clopidogrel, multiple dose (5 mg, 10 mg or 20 mg) study, and study in aspirin-treated patients with atherosclerotic vascular disease (75 mg), completed. Studies demonstrated significantly higher and more consistent inhibition of platelet aggregation (IPA) compared to both placebo and clopidogrel (Sankyo pr, 3/2005).

#### Status

Phase	Region	Developer(s)	Marketer(s)
Pending Approval	USA	Daiichi Sankyo Co., Ltd.; Eli Lilly and Company	Daiichi Sankyo Co., Ltd.; Eli Lilly and Company
Pending Approval	Europe	Daiichi Sankyo Co., Ltd.; Eli Lilly and Company	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.
Phase II	Canada	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.
Phase II	Israel	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.
Phase I	Japan	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.

#### Preparation and Method of Delivery

Oral - tablet

#### US Approval Process

FDA Approval	Approval Date	Approval Type	NDA or BLA #	Supplement #	Chemical Type	Review Type
		New Drug Application (NDA)				Priority
<b>Original Applicant</b>	Sankyo Co., Ltd.					
<b>Description</b>	The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) will review prasugrel during an advisory committee hearing on 3 Feb 2009 (Daiichi Sankyo pr, 12/2008). Three issues seem to have delayed an FDA decision: increase in bleeding and concerns of related deaths in the treatment arm, more cancers discovered in the prasugrel group compared to Plavix in the TRITON study and formulation issue related either to the active ingredient or the excipient substance (Pink Sheet Daily, 10/2008). FDA's decision on prasugrel will not come before Mar 2009 (Pink Sheet Daily, 10/2008). FDA extended review period until 26 Sep 2008. Priority review granted Feb 2008 (Eli Lilly pr, 6/2008).					
<b>Application Submission</b>	<b>Submission Date</b>	<b>Application Type</b>	<b>User Fee Deadline Date</b>	<b>Complete Review Date</b>	<b>Approval Status</b>	
	26 Dec 2007	New Drug Application (NDA)	26 Sep 2008		Approvable	

#### Non-US Regulatory

Country	Filing Date	Filing Status	Approval Date(s)
Europe	Feb 2008	The CHMP issued positive opinion for approval of prasugrel (Eli Lilly pr, 12/2008). MAA submitted for the prevention of atherothrombotic events in patients with acute coronary syndrome managed with percutaneous coronary intervention (PCI) (Daiichi Sankyo pr, 2/2008).	

### Indication

Management of patients with acute coronary syndrome (ACS), including unstable angina and heart attacks

### Status Comment

Phase III TRILOGY ACS study initiated Jun 2008 ongoing in the US, Australia, Austria, Belgium, Canada, Chile, Colombia, Hungary, India, Italy, Lithuania, Netherlands, New Zealand, South Africa and Sweden to compare prasugrel vs. clopidogrel in a medically managed UA/NSTEMI ACS population. Primary endpoint: reduction in risk of the composite endpoint of first occurrence of CV death, MI, or stroke; secondary endpoints: risk of the first occurrence of CV death and MI, risk of the first occurrence CV death, MI, stroke, or re-hospitalization for recurrent UA, risk of the of first occurrence of all-cause death, platelet aggregation measures, biomarker measurements of inflammation/hemodynamic stress, genotyping related to drug metabolism, economic and quality of life (clintrial.gov, as of 12/2008). Companies anticipated initiation of Phase III study Q2:2008 (Daiichi pr, 11/2007). Two Phase II trials initiated Jul 2006 in the US and Mar 2007 in France were suspended until protocol amendments can be completed and approved. The amendments are due to preliminary results from pharmacokinetic analyses, indicating that a dose adjustment may be appropriate for certain subpopulations. Patient enrollment will resume as soon as additional analyses of pharmacokinetic and clinical data are completed, and protocols are amended and approved by institutional review boards (Eli Lilly pr, 10/2007).

### Status

Phase	Region	Developer(s)	Marketer(s)
Phase III	USA	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.
Phase III	Canada	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.
Phase III	Australia	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.
Phase III	Austria	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.
Phase III	Belgium	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.
Phase III	Chile	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.
Phase III	Colombia	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.
Phase III	India	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.
Phase III	Italy	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.
Phase III	Netherlands	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.
Phase III	South Africa	Daiichi Sankyo Co., Ltd.	Daiichi Sankyo Co., Ltd.
Phase III	Sweden	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.	Eli Lilly and Company; Daiichi Sankyo Co., Ltd.

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