

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204958Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Final Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: January 21, 2014

Reviewer: Somya Dunn, M.D.  
Division of Risk Management (DRISK)

Team Leader: Kim Lehrfeld, Pharm.D., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Drug Name(s): Cangrelor

Therapeutic Class: P2Y<sub>12</sub> platelet inhibitor

Dosage and Route: Indication: Percutaneous Coronary Intervention—30 µg/kg intravenous (IV) bolus followed by 4 µg/kg/min intravenous infusion for at least two hours  
Indication: Bridging—0.75 µg/kg/min intravenous infusion

Application Type/Number: NDA/204-958

Submission Number: Supporting Document 1 (Sequence 0000)

Applicant/sponsor: The Medicines Company

OSE RCM #: 2013-1144

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## 1 INTRODUCTION

The purpose of this document is to assess the need for a Risk Evaluation and Mitigation Strategy (REMS) for the cangrelor NDA 204-958. The Sponsor, The Medicines Company, submitted this NDA on April 30, 2013. The NDA is currently under review in the Division of Cardiovascular and Renal Products (DCRP).

Cangrelor is an intravenous P2Y<sub>12</sub> platelet inhibitor. P2Y<sub>12</sub> is an adenosine diphosphate (ADP) chemoreceptor on platelet cell membranes. Cangrelor's proposed indication is for the reduction of thrombotic events (including stent thrombosis) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). The Sponsor is also proposing a "bridging" indication. This indication is to maintain P2Y<sub>12</sub> inhibition in acute coronary syndrome (ACS) patients, or patients with stents, who are at increased risk for thrombotic events when oral P2Y<sub>12</sub> therapy is interrupted due to surgery.

### 1.1 BACKGROUND

Cangrelor is part of the class of medications, P2Y<sub>12</sub> inhibitors or Thienopyridines (approved in the U.S. for oral use are Plavix®, Effient® and Brilinta®). Oral P2Y<sub>12</sub> inhibitors reduce cardiovascular events in patients with ACS and in patients who have coronary stent placement procedures. The Sponsor asserts that currently approved oral platelet P2Y<sub>12</sub> inhibitors have several limitations in the acute treatment phase of patients with cardiovascular disease who require PCI or surgery. This includes delayed onset of action and poor reversibility. These can result in thrombotic complications during and immediately after PCI. In addition, continuing oral P2Y<sub>12</sub> inhibitors to reduce the risk of thrombosis after stenting leads to a high risk situation in patients that end up requiring surgery since continuing treatment increases the risk of bleeding. On the other hand, if oral P2Y inhibitors are held for surgery or PCI, there is an increased risk of thrombosis.

Cangrelor is an intravenous (IV), direct-acting, P2Y<sub>12</sub> receptor antagonist that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation. Cangrelor provides fast onset and offset and reversible binding with a half-life of three to six minutes.

For the PCI indication the proposed dose of cangrelor is 30 µg/kg intravenous (IV) bolus prior to PCI followed immediately by a 4 µg/kg/min IV infusion for at least two hours (or duration of procedure whichever is longer). For the bridging indication, the proposed dose is 0.75 µg/kg/min IV as soon as possible following discontinuation of oral P2Y<sub>12</sub> inhibitors until one hour prior to surgery.

The submission for cangrelor did not contain a proposed Risk Evaluation and Mitigation Strategy. Of note, Brilinta and Effient were approved with a REMS for the risk of bleeding; however the REMS were removed in 2012 and 2013, respectively. This is discussed in detail in Section 2.3 Safety Concerns.

### 1.2 REGULATORY HISTORY

The End of Phase 2 meeting to discuss the design of the Phase 3 clinical trials at length occurred on November 9, 2009. Additional meetings to discuss the NDA occurred on

May 14, 2012, August 15, 2012, November 20, 2012 (official PreNDA meeting), and February 25, 2013. These meetings included discussion on efficacy, trial design, data submission and statistical issues. The safety endpoint of bleeding was discussed at the meetings as well including how to capture and measure this endpoint. At the PreNDA meeting in November 2012, the Sponsor stated that they did not plan to develop a REMS and asked for Agency feedback. The Agency responded that the need for a REMS would be determined during the NDA review process.

## **2 MATERIALS REVIEWED**

### **2.1 MATERIALS INFORMING THIS REVIEW**

- Clinical Overview, The Medicines Company, received on April 30, 2013 (Supporting Document1, Sequence 0000)
- Summary of Clinical Safety The Medicines Company, received on April 30, 2013 (Supporting Document1, Sequence 0000)
- Integrated Summary of Safety The Medicines Company, received on April 30, 2013 (Supporting Document1, Sequence 0000)
- Summary of Clinical Efficacy The Medicines Company, received on April 30, 2013 (Supporting Document1, Sequence 0000)
- Annotated Draft Labeling Text, The Medicines Company, received on August 30, 2013 (Supporting Document 15, Sequence 0014)
- Review of Brilinta REMS modification Supplement 9, Dr. Danielle Smith, October 17, 2013

### **2.2 OVERVIEW OF CLINICAL PROGRAM**

Cangrelor treatment has been evaluated in 16 clinical trials, including four pivotal trials. Data from the four randomized, double-blind clinical trials were conducted in over 25,000 patients with coronary artery disease (CHAMPION PHOENIX, CHAMPION PLATFORM, CHAMPION PCI, and BRIDGE).

The patients who received the highest dose ( $\geq 4.0$   $\mu\text{g}/\text{kg}/\text{min}$ ) for the shortest duration ( $< 24$  hours) represent the majority of exposures ( $N=12,787$ , 99.12%); these patients are predominantly in the CHAMPION studies. Patients receiving the 0.75  $\text{mg}/\text{kg}/\text{min}$  dose were in the BRIDGE study, with duration of exposures ranging from 48 hours up to  $\geq 72$  hours. Doses up to 4.0  $\mu\text{g}/\text{kg}/\text{min}$  with durations up to 72 hours were also given (placebo-controlled studies). In all studies, there were a total of 13,301 patients receiving cangrelor and 12,861 control patients.

Primary efficacy data was derived from CHAMPION PHOENIX. In this study, the use of cangrelor during PCI significantly reduced (relative risk reduction [RRR] 22%) the primary composite endpoint of all-cause mortality (death/myocardial infarction (MI)/ischemia driven revascularization (IDR) and stent thrombosis) compared to clopidogrel ( $p=0.005$ ).

The BRIDGE trial was conducted in patients with ACS or patients with coronary stents who were at increased risk of thrombotic events (such as ST) following discontinuation

of oral platelet P2Y<sub>12</sub> inhibitor treatment prior to cardiac surgery. According to the Sponsor, 98.8% of patients treated with cangrelor achieved the target level of platelet inhibition until the time of surgery compared to 19.0% of patients treated with placebo (p<0.001).

### 2.3 SAFETY CONCERNS

#### Bleeding

P2Y<sub>12</sub> inhibitors or Thienopyridines are known to have an increased risk of bleeding. Effient and Brilinta have a boxed warning for bleeding risk. Both Effient and Brilinta had a REMS at approval to ensure that the benefits of treatment outweighed the risk of bleeding. The REMS consisted of a Medication Guide, communication plan and timetable for submission of assessments. The Effient REMS also emphasized the importance of proper patient selection in order to address the increased risk of hemorrhagic bleeding in patients with a history of stroke or transient ischemic attacks (TIA). The Brilinta REMS had an additional goal as well—to address a loss of efficacy when administered with aspirin, which was not seen with cangrelor. Both REMS requirements were released when the communication plan activities were complete and the Agency determined the goals of the REMS had been met; Effient was released in March 2012 and Brilinta in October 2013. For full details, please see Dr. Mary Ross Southworth's REMS Memorandums for both applications.

Bleeding was the most common adverse event (AE) seen in the clinical program for cangrelor. The GUSTO (Global Use of Strategies to Open Occluded Arteries—mild, moderate and severe or life-threatening categories) bleeding scale was measured in the CHAMPION (PHOENIX, PLATFORM, and PCI) and BRIDGE clinical trials. Please see Dr. Nhi Beasley's review for a detailed discussion of safety including evaluation of bleeding risk.

Dr. Beasley reports that non-CABG related bleeding rates were higher for patients treated with cangrelor than clopidogrel (15.5% vs. 10.9%) in CHAMPION PHOENIX. This includes a higher rate of severe GUSTO AEs in the cangrelor group (0.18% vs. 0.11%).

The Sponsor reports that the BRIDGE trial, the main safety endpoint of excessive CABG-related bleeding was similar for cangrelor and placebo- treated patients (12/102, 11.8% vs. 10/96, 10.4%, respectively).

#### Reviewer's Comment

*If approved, cangrelor will be the fourth approved drug in this class. Although the risk of bleeding is evident with cangrelor, it is an expected AE with all drugs in this class. Cangrelor is proposed for short term, inpatient, IV infusion use while other medications in this class are approved for long-term oral use. Therefore, there is greater assurance with cangrelor, which is administered in an inpatient setting, than with other oral P2Y<sub>12</sub> inhibitor that sufficient monitoring and treatment of a bleeding event will occur. Furthermore, Brilinta and Effient labeling contain a boxed warning for bleeding and were subsequently initially approved with a REMS to address this serious risk. Since it will be used as an inpatient short term infusion, the division is not planning to recommend a boxed warning for bleeding for cangrelor at this time.*

### Other Safety Concerns

Plavix has a boxed warning for diminished effectiveness in poor metabolizers due to activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. However, Plavix needs to be activated to its active moiety by metabolism in the body (by CYP2C19). Cangrelor, on the other hand, is active on its own and does not require metabolic activation.

An increased rate of dyspnea is also a class effect and is a W&P for Brilinta. Dyspnea was seen in the cangrelor clinical program and was a common AE (1.3% vs. 0.4% in control). The Sponsor addresses this risk in the label in discussion of AEs, not as a W&P. The details of the label are still under discussion with DCRP.

The most common AE reported in the cangrelor arm in all the studies that occurred in at least 0.5% more patients treated with cangrelor is hypotension (1.9% vs. 1.4%).

### Deaths and Other SAEs

In the total pooled safety population, fatal bleeding events within 30 days of dosing were low and balanced in cangrelor (8/13301, 0.1%) versus control group (9/12861, 0.1%). Deaths after 30 days were low and were similar in both the cangrelor and control groups (5 vs. 6, respectively). In all studies, there were 306 deaths in the cangrelor group (2.3%) and 328 in control (2.6%). For deaths by System Organ Class and for other serious adverse events (SAEs), the overall incidence across all studies was low and similar in both the cangrelor and control groups.

Overall, the safety data do not indicate that there are unexpected AEs or unusual rates of AEs associated with cangrelor that would warrant a REMS.

## **3 DISCUSSION**

A higher rate of bleeding was observed in patients taking cangrelor. Bleeding is an expected AE in this class of medications. Since cangrelor is proposed as a short term, IV infusion, professional labeling is sufficient to address this risk. Other AEs observed in the clinical program in a higher incidence in cangrelor treated patients, such as dyspnea, can also be addressed with professional labeling. Most AE rates were similar between cangrelor and control.

The safety profile of cangrelor does not present any new or unique safety signals that would warrant a REMS.

## **4 CONCLUSION/RECOMMENDATIONS**

In conclusion, risk mitigation measures beyond professional labeling are not warranted for cangrelor. The safety profile for cangrelor is consistent with currently approved products, which do not have a REMS. There were no new or unique safety concerns associated with cangrelor in the pivotal trials.

Should DCRP raise further concerns with the risks outlined above or identify additional risks associated with cangrelor warranting more extensive risk mitigation or a formal REMS, please notify DRISK.

This memo serves as the DRISK review for NDA 204958.

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