IMPORTANT LABEL UPDATES: PLAVIX®, EFFIENT®, BRILINTA®

- The PIs for clopidogrel, prasugrel, and ticagrelor have all been recently updated to include safety information regarding a drug-drug interaction involving opioid co-administration
- Updates are specifically related to the risk of delayed and decreased absorption of these drugs when opioids are administered concomitantly

PLAVIX® (clopidogrel bisulfate) Prescribing Information[1]

7.2 Opioids

As with other oral $P2Y_{12}$ inhibitors, coadministration of opioid agonists delay and reduce the absorption of clopidogrel, presumably because of slowed gastric emptying, resulting in reduced exposure to its metabolites *[see Clinical Pharmacology (12.3)].* Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring coadministration of morphine or other opioid agonists.

12.3 Pharmacokinetics (excerpt)

Opioids - Coadministration of 5 mg intravenous morphine with 600 mg loading dose of clopidogrel in healthy adults decreased the AUC and C_{max} of clopidogrel's thiol metabolites by 34%. Mean platelet aggregation was higher up to 2 to 4 hours with morphine coadministration.

EFFIENT® (prasugrel) Prescribing Information[2]

7.3 Opioids

As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of prasugrel's active metabolite presumably because of slowed gastric emptying *[see Clinical Pharmacology (12.3)].* Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

12.3 Pharmacokinetics (excerpt)

Morphine - Co-administration of 5 mg intravenous morphine with 60 mg loading dose of prasugrel in healthy adults decreased the C_{max} of prasugrel's active metabolite by 31% with no change in AUC, T_{max}, or inhibition of ADP-induced platelet aggregation. ADP induced platelet aggregation was higher up to 2 hours following 60 mg loading dose of prasugrel in stable patients more than 1 year after an ACS who were co-administered morphine. In the patients with a 2-hour delay in the onset of platelet aggregation (5 of 11), T_{max} was delayed and prasugrel active metabolite levels were significantly lower at 30 min (5 vs 120 ng/mL) following co-administration with morphine.

BRILINTA® (ticagrelor) Prescribing Information[3]

7.4 Opioids

As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of ticagrelor and its active metabolite presumably because of slowed gastric emptying *[see Clinical Pharmacology (12.3)].* Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

12.3 Pharmacokinetics (excerpt)

Co-administration of 5 mg intravenous morphine with 180 mg loading dose of ticagrelor decreased observed mean ticagrelor exposure by up to 25% in healthy adults and up to 36% in ACS patients undergoing PCI. T_{max} was delayed by 1-2 hours. Exposure of the active metabolite decreased to a similar extent. Morphine co-administration did not delay or decrease platelet inhibition in healthy adults. Mean platelet aggregation was higher up to 3 hours post loading dose in ACS patients co-administered with morphine.

Co-administration of intravenous fentanyl with 180 mg loading dose of ticagrelor in ACS patients undergoing PCI resulted in similar effects on ticagrelor exposure and platelet inhibition.

Characteristics of $P2Y_{12}$ platelet inhibitors

	IV Administration	Oral Administration		
	KENGREAL[4]	**Ticagrelor**[3]	**Prasugrel**[2]	**Clopidogrel**[1]
Compound class	ATP analogue	CPTP	Thienopyridine	Thienopyridine
Action	Direct acting	Direct acting*	Prodrug	Prodrug
Onset of PD effect	~2 min†	30 min†	30 min†	2 hours
Time to maximal effect	~2 min	~2 hours	~2 hours	3-7 days‡
Maximum platelet inhibition	>98%[5]	88%	~80%	40%-60%§
Reversible $P2Y_{12}$ receptor binding	YES	YES	NO	NO
Half-life	3-6 min	~7 hours*	~7 hours	~6 hours¶
Platelet function returns to baseline after discontinuation	~1 hour	5 days	5-9 days	5 days

Clinical studies have not established that IV administration or pharmacological characteristics result in superior efficacy or safety based on clinically relevant end points.

*Ticagrelor has an active metabolite with a half-life of 9 hours. †1st time point at which inhibition of platelet aggregation was measured. ‡Based on 75 mg daily dose, when platelet inhibition reaches steady state. Time to maximal effect for a loading dose is not provided in the prescribing information. §40% to 60% refers to average inhibition at steady state. ¶Active metabolite of clopidogrel has a half-life of 30 minutes.

Indication

KENGREAL® (cangrelor) for Injection is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

Important Safety Information

KENGREAL® for Injection is contraindicated in patients with significant active bleeding.

KENGREAL® is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to cangrelor or any component of the product.

Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL®, increase the risk of bleeding. In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL® than with clopidogrel. Bleeding complications with KENGREAL® were consistent across a variety of clinically important subgroups. Once KENGREAL® is discontinued, there is no antiplatelet effect after an hour.

The most common adverse reaction is bleeding.

Please see accompanying Full Prescribing Information.

PD, pharmacodynamic; CPTP, cyclopentyl-triazolopyrimidine.

References: 1. Plavix® Prescribing Information, Bristol-Myers Squibb/Sanofi, October 2018. **2.** Effient® Prescribing Information, Eli Lilly and Co., March 2018. **3.** Brilinta® Prescribing Information, AstraZeneca, March 2018. **4.** KENGREAL [package insert]. Cary, NC: Chiesi USA, Inc.; 2016. **5.** Data on file. Chiesi USA, Inc.

KENGREAL®
(cangrelor) for injection

For more information, please visit
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