



Month/Year of Review: November 2011

Generic Name: Prasugrel

Brand Name: Effient™

PDL Class: Antiplatelet

Preferred: aspirin, aspirin/dipyridamole, clopidogrel, dipyridamole

Non-Preferred: ticlopidine, prasugrel (pending review), ticagrelor (pending review)

End date of literature search: 4th Quarter 2010

Manufacturer: Eli Lilly & Daiichi Sankyo

Dossier received: Yes, via DERP review

Comparator Therapies: clopidogrel

FDA Approved Indications: To reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

Summary: A recent Drug Effectiveness Review Project (DERP) systematic, comparative effectiveness review found high-strength evidence that prasugrel reduced target-vessel revascularization more than clopidogrel at 15 months in patients with ACS undergoing coronary revascularization.¹ There was moderate- to high-strength evidence of no significant differences between prasugrel and clopidogrel in the most important effectiveness outcomes including: all-cause mortality and cardiovascular mortality outcomes. Moderate-strength evidence indicated that more major bleeding occurred with prasugrel use. There was no evidence meeting inclusion criteria for prasugrel used for other indications (ACS managed medically, secondary stroke prophylaxis, peripheral vascular disease or primary prevention of cardiovascular events in high risk individuals).

PDL Placement Recommendation:

Required _____

Recommended depending on price X

Recommended with restriction X

Not recommended _____

Utilization Control Recommendations:

OHP Coverage _____

Step Therapy X

Dose Limit _____

Age Restriction X

Therapy Length Limit _____

Gender Restriction _____

Evidence Grade¹:

Effectiveness for ACS managed with PCI only
Safety

Moderate to High
Moderate

BACKGROUND/CURRENT LANDSCAPE

Antiplatelet drugs are used to prevent cardiovascular events and premature death in patients with multiple risk factors and in patients who have experienced Acute Coronary Syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction), transient ischemic attacks or thromboembolic stroke, or symptomatic peripheral arterial disease. Aspirin has been considered the gold standard. Aspirin is effective in reducing the occurrence of major cardiovascular events including death, recurrent myocardial infarction, recurrent angina, or progression to severe angina and nonfatal stroke. Several practice guidelines have been published that provide recommendations regarding the role of aspirin.^{2,3,4,5,6,7} Newer antiplatelet agents, and in particular clopidogrel, are used as an adjunct to or substitution for aspirin in specific clinical situations, particularly in those who have contraindications to aspirin. However, the role of individual antiplatelet agents relative to each other is still evolving. There is reported variability in patient platelet aggregation response to clopidogrel, though the risk of adverse outcomes due to this has yet to be fully elucidated.^{8,9,10}

CLINICAL PHARMACOLOGY

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y₁₂ class of ADP receptors on platelets.¹¹

¹ High – results unlikely to change with further research; Moderate – results may change with further research; Low- results likely to change; Insufficient – effect can't be estimated with available evidence:

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints: 1) All cause mortality
 2) Cardiovascular (CV) mortality
 3) Target-vessel revascularization (TVR)
 4) Non-CABG Major Bleeding (TIMI)
 5) Withdrawals due to adverse events

Primary Study Endpoint: 1) Composite of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke

Evidence Table

Ref./ Study Design ^a	Drug Regimens	Patient Population	N	Duration	Efficacy Results ^b	ARR / NNT ^c	Safety Results (CI, p-values)	ARR / NNH ^c	Quality Rating ^d ; Comments
TRITON-TIMI 38 ²									
Wiviott SD, et. al. Phase III, RCT, DB, PG	P:Prasugrel 60 mg load, followed by 10 mg QD C:Clopidogrel 300 mg load, followed by 75 mg QD x 6 to 15 months (median 14.5 months) ASA 75-162mg was required.	Mean Age: 61 yrs Male: 74% White: 92.5% ACS patients with moderate to high risk (74% NSTEMI, 26% STEMI) who received percutaneous coronary interventions.	P: 6813 C: 6076	Outcomes assessed @ 15 months	<u>All Cause Mortality:</u> P: 188 (3.0%) C: 197 (3.2%) HR: 0.95 95% CI: 0.78 - 1.16 P=0.64 <u>CV Mortality:</u> P: 133 (2.1%) C: 150 (2.4%) HR: 0.89 95% CI: 0.70-1.12 P=0.31 <u>TVR:</u> P: 156 (2.5%) C: 233 (3.7%) HR: 0.66 95% CI: 0.54-0.81 P=<0.001	NS NS ARR: 1.2% NNT: 83	<u>Major Bleeding:</u> P: 146 (2.4%) C: 111 (1.8%) RR: 1.32 95% CI 1.03-1.68 P=0.03 <u>Withdrawals due to Adverse events:</u> P: NR (7.2%) C: NR (6.4%) RR: 1.14 95% CI: 1.00-1.29	ARR: 0.5% NNH: 167 NS	Good Quality; Study was powered for composite efficacy outcome only. The results from component outcomes of interest and safety endpoints need to be interpreted with caution.

^aStudy design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.

^bResults abbreviations: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval

^cNNT/NNH are reported only for statistically significant results

^dQuality Rating: (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

TIMI = Thrombolysis In Myocardial Infarction bleeding criteria NSTEMI = non-ST-elevation myocardial infarction STEMI= ST-elevation myocardial infarction

Summary of Findings –

Prasugrel was compared to clopidogrel in the phase 3 trial, TRITON-TIMI 38.¹² It included 13,608 patients with moderate- to high-risk acute coronary syndromes (74% unstable angina or non-ST segment elevation myocardial infarction, 26% ST segment elevation myocardial infarction) who received percutaneous coronary interventions. It was a good-quality, multi-site, head-to-head trial. Two other fair-quality head-to-head trials^{13,14} were smaller (n= 201 and n=905) and shorter (14 days and 30 days) studies to establish dose and had too few events to evaluate. The primary efficacy outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. All outcomes were assessed at 15 months.

There was moderate- to high-strength evidence of no significant differences between prasugrel and clopidogrel in the most important effectiveness outcomes of all-cause mortality (hazard ratio, 0.95; 95% CI, 0.78 to 1.16) and cardiovascular mortality (hazard ratio, 0.89; 95% CI, 0.70 to 1.12) outcomes. The study was not powered or designed to detect differences in these secondary outcomes. However despite the lack of power, it provided high-strength evidence of superiority of prasugrel over clopidogrel for prevention of target vessel revascularization post-percutaneous coronary intervention (2.5% compared with 3.7%; hazard ratio, 0.66; 95% CI, 0.54 to 0.81; P<0.001; absolute risk reduction, 1.2%; number needed to treat, 83). Moderate-strength evidence indicated that there was more major bleeding and no difference in withdrawal due to adverse events with prasugrel.

There was no evidence for prasugrel used for other indications (ACS managed medically, secondary stroke prophylaxis, peripheral vascular disease or primary prevention of cardiovascular events in high risk individuals).

The DERP review¹ did not find studies that met inclusion criteria and evaluated differences in all cause mortality, CV mortality, or target-vessel revascularization rates between clopidogrel and prasugrel when used concomitantly with proton pump inhibitors. Similarly, there was no eligible randomized control trials found that assessed effectiveness differences between the clopidogrel and prasugrel based upon genotype. There continues to be controversy about the clinical impact of both concomitant use of clopidogrel with proton pump inhibitors and in certain genotypes.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications): Significant, sometimes fatal, bleeding. Do not use in patients with active pathological bleeding or those with a history of transient ischemic attack or stroke. Not recommended in patients >75 years old due to increased risk of fatal and intracranial bleeding coupled with uncertain benefit except in high-risk patients (diabetes or prior MI) where the effect appears to be greater and its use may be considered. Additional risk factors for bleeding include: Body weight < 60kg, propensity to bleed, concomitant use of medications that increase the risk of bleeding.¹¹

Tolerability: Dropout rates for prasugrel (7.2%) compared to clopidogrel (6.4%) were not significantly different. Rate of discontinuance not related to hemorrhage was prasugrel (4.7%) compared to clopidogrel (5.0%), p=0.37. Severe thrombocytopenia occurred in 17 (0.3%) prasugrel patients and 18 (0.3%) clopidogrel patients, p=0.86. Neutropenia occurred in 2 (<0.1%) prasugrel patients compared to 10 (0.2%) clopidogrel patients, p=0.02. Colonic neoplasms occurred in 13 (0.2%) prasugrel patients compared to 4 (0.1%) clopidogrel patients, p=0.03.¹¹

Pregnancy/Lactation rating: B - There are no adequate and well-controlled studies of Effient use in pregnant women.¹¹

Unanswered safety questions: A major concern is the bleeding risk in general clinical use given the increased risk in special populations coupled with limited benefit in all but those with higher risk.¹ There was an increased rate of colonic neoplasm in the phase III study but it is unclear if these observations are causally-related or are random occurrences.¹¹

Dose Index (efficacy/toxic): The effective dose is 60mg load followed by 10mg daily. The human toxic dose has not been published. The lethal dose in rats is 2000mg/kg.¹¹

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	ISMP	Clinical Judgment
LA/SA for prasugrel (generic)	pravastatin, propranolol	None	None	
LA/SA for Effient™(brand)	None	None	None	Effexor

ADVERSE REACTIONS¹¹Table 1: Non-CABG-Related Bleeding^a (TRITON-TIMI 38)

	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)	p-value
TIMI Major or Minor bleeding	4.5	3.4	p=0.002
TIMI Major bleeding ^b	2.2	1.7	p=0.029
Life-threatening	1.3	0.8	p=0.015
Fatal	0.3	0.1	
Symptomatic intracranial hemorrhage (ICH)	0.3	0.3	
Requiring inotropes	0.3	0.1	
Requiring surgical intervention	0.3	0.3	
Requiring transfusion (≥ 4 units)	0.7	0.5	
TIMI Minor bleeding ^b	2.4	1.9	p=0.022

^a Patients may be counted in more than one row.

^b See 5.1 for definition.

Table 2: Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)

	Major/Minor		Fatal	
	Effient (%)	Clopidogrel (%)	Effient (%)	Clopidogrel (%)
Weight < 60kg (N=308 Effient, N=356 clopidogrel)	10.1	6.5	0.0	0.3
Weight \geq 60kg (N=6373 Effient, N=6299 clopidogrel)	4.2	3.3	0.3	0.1
Age < 75 years (N=5850 Effient, N=5822 clopidogrel)	3.8	2.9	0.2	0.1
Age \geq 75 years (N=891 Effient, N=894 clopidogrel)	9.0	6.9	1.0	0.1

Table 3: CABG-Related Bleeding^a (TRITON-TIMI 38)

	Effient (%) (N=213)	Clopidogrel (%) (N=224)
TIMI Major or Minor bleeding	14.1	4.5
TIMI Major bleeding	11.3	3.6
Fatal	0.9	0
Reoperation	3.8	0.5
Transfusion of ≥ 5 units	6.6	2.2
Intracranial hemorrhage	0	0
TIMI Minor bleeding	2.8	0.9

^a Patients may be counted in more than one row.

Table 4: Non-Hemorrhagic Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group

	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)
Hypertension	7.5	7.1
Hypercholesterolemia/Hyperlipidemia	7.0	7.4
Headache	5.5	5.3
Back pain	5.0	4.5
Dyspnea	4.9	4.5
Nausea	4.6	4.3
Dizziness	4.1	4.6
Cough	3.9	4.1
Hypotension	3.9	3.8
Fatigue	3.7	4.8
Non-cardiac chest pain	3.1	3.5
Atrial fibrillation	2.9	3.1
Bradycardia	2.9	2.4
Leukopenia ($< 4 \times 10^9$ WBC/L)	2.8	3.5
Rash	2.8	2.4
Pyrexia	2.7	2.2
Peripheral edema	2.7	3.0
Pain in extremity	2.6	2.6
Diarrhea	2.3	2.6

DOSE & AVAILABILITY¹¹

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10mg (5mg dose available but not studied prospectively)	Tablet	Oral	60mg load, followed by 10mg daily	None; limited experience in patients with end-stage renal disease	None moderate hepatic impairment (Child-Pugh Class A and B). Not studied in severe hepatic disease	Safety and effectiveness not established	Safety and effectiveness in patients ≥ 75 years old is uncertain and generally not recommended	Consider lowering dose to 5mg daily in patients weighing <60 kg. The safety and effectiveness of this dose has not been prospectively studied. Can be administered without regard to food.

PHARMACOKINETICS¹¹

Parameter	Result
Oral Bioavailability	$\geq 79\%^*$
Protein Binding	98%^
Elimination	68% urine, 27% feces
Half-Life	2-15 hours^
Metabolism	S-methylation or conjugation with cysteine

*prasugrel is a prodrug and rapidly metabolized to active and inactive metabolites primarily by CYP3A4 and CYP2B6.

^active metabolite

ALLERGIES/INTERACTIONS¹¹

Drug-Drug: Warfarin: increased risk of bleeding¹¹; NSAIDs (chronic): increased risk of bleeding¹¹; Can be administered with inducers or inhibitors of cytochrome P450, aspirin 75-325mg daily, heparin, GPIIb/IIIa inhibitors, statins, digoxin and drugs that elevate gastric pH (including proton pump inhibitors and H2-blockers)¹¹

Food-Drug: No food-drug interactions have been reported.¹¹

APPENDIX:
Suggested PA Criteria

Platelet Inhibitors

Goal(s):

- Promote safe and effective therapies for platelet inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	Yes: Go to #3.	No: Pass to RPh, Deny for OHP Coverage.
3. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> • Most preferred products do not require PA (e.g. aspirin, clopidogrel) 	Yes: Inform provider of covered alternatives in class http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	No: Go to #4
4. Is the request for prasugrel AND one of the following: <ul style="list-style-type: none"> ≥75 years old ≤ 60 kg s/p stroke or TIA 	Yes: Pass to RPh, Deny for appropriateness.	No: Go to #5
5. Is the patient unable to take clopidogrel due to one of the following: <ul style="list-style-type: none"> - clopidogrel allergy - contraindications to clopidogrel therapy (document) - drug-drug interactions (document) - intolerable side effects 	Yes: Approve up to 1 year	No: Deny. Recommend clopidogrel trial

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