PRASUGREL (Effient®) CLINICIAN SUMMARY

Mechanism of Action: Selective and irreversibly bound antagonist of the $P2Y_{12}$ receptor. Inhibits ADP-mediated platelet activation and aggregation.

BACKGROUND

Prasugrel is a 2nd generation thienopyridine.

Place in Therapy

Use of prasugrel at UHN is limited to patients without prior stroke or TIA presenting with STEMI or intermediate to high risk ACS, including NSTEMI and UAP, who have been selected to undergo invasive management.

Prasugrel provides no benefit over clopidogrel in patients with ACS managed conservatively (TRIOLOGY-ACS).[1] Compared to clopidogrel, prasugrel is considered to provide more rapid, more consistent and more potent platelet inhibition at the cost of higher rates of bleeding. Use is therefore contraindicated in patients with prior stroke or TIA and should be used with caution in patients ≥75 years of age or under 60 kg.

Summary of Endpoints from TRITON-TIMI38:[2]

In patients with ACS managed invasively, use of prasugrel compared with clopidogrel was associated with a significant reduction in the rate of the primary endpoint of cardiovascular death/MI/stroke along with a significant reduction in the rate of urgent vessel revascularization and stent thrombosis.

End Point	Prasugrel (n=6813)	Clopidogrel (n=6795)	HR (95% CI)	P Value
CV death/non-fatal MI/ non-fatal stroke	**643 (9.9%)**	**781 (12.2%)**	**0.81 (0.73-0.90)**	**<0.001**
Death from any cause	188 (3%)	197 (3.2%)	0.95 (0.78-1.16)	0.64
Urgent target vessel revascularization	156 (2.5%)	233 (3.7%)	0.66 (0.54-0.81)	<0.001
Stent thrombosis	68 (1.1%)	142 (2.4%)	0.48 (0.36-0.64)	<0.001

Dosing: 60 mg PO loading dose, then 10 mg PO once daily

Dose Adjustments: No dose adjustment is recommended in renal impairment or in mild to moderate hepatic impairment. Use is contraindicated in patients with severe hepatic impairment.

Administration

Supplied as 10 mg tablets.

- May be taken without regard to food.
- Tablet may be crushed if administered immediately by mouth or gastric tube. For jejunostomy (J) tube, consult Pharmacy.
- Tablets are not scored and should not be broken or divided for dosing purposes. To maintain product stability, tablets should be stored in their original aluminum foil blister pack.

Switching from prasugrel to clopidogrel: Refer to *Antiplatelet Therapy Switching-Clinician Guide.*

PHARMACOLOGIC PROFILE

Onset of Platelet Aggregation Inhibition: <30 minutes with 60 mg loading dose

PRASUGREL (Effient®) CLINICIAN SUMMARY

Peak Effect: 0.5-1.5 hours
Duration of Effect: >3 days; platelet aggregation will return to baseline 5-9 days after discontinuation.

Bioavailability: >79% absorbed

Elimination: 68% urine, 27% feces

CONTRAINDICATIONS

- history of TIA or stroke
- active bleeding
- severe hepatic impairment (Child-Pugh Class C)
- hypersensitivity

PRECAUTIONS

- Age ≥75 years
- Weight <60 kg

  Note: In subgroup analyses of the TRITON-TIMI 38 trial, these patients were found to have increased risk of bleeding with prasugrel, and the net benefit over clopidogrel was unclear.[5]
- High bleeding risk due to recent history of bleed/trauma, or concurrent medications (i.e., oral anticoagulants, NSAIDS)
- **Pharmacodynamic drug interactions**
  - Concomitant use of other antiplatelet agents (e.g., ASA, clopidogrel) or other anticoagulants (warfarin, low molecular weight heparins, unfractionated heparin, fondaparinux, dabigatran) will increase the risk of bleeding.
  - During clinical studies, prasugrel was commonly administered with ASA, heparin, digoxin, low molecular weight heparin, proton pump inhibitors, statins, beta-blockers as needed for concomitant conditions, and did not produce any evidence of clinically significant drug interactions.
- **Pharmacokinetic drug interactions**
  - Prasugrel can be concomitantly administered with drugs metabolized by cytochrome P450 enzymes or with drugs that are inducers or inhibitors of cytochrome P450 enzymes. In vitro studies demonstrate that prasugrel's metabolites are not likely to cause significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A, or induction of CYP1A2 or CYP3A.

ADVERSE EFFECTS

- **bleeding** (contusion, hematoma, epistaxis), **GI hemorrhage**
- **fever, musculoskeletal pain, fatigue** reported in TRITON-TIMI 38

Summary of safety endpoints from TRITON-TIMI 38:

Compared to clopidogrel, use of prasugrel was associated with significantly higher rates of:

- CABG-related TIMI major bleeding
- non-CABG-related TIMI major bleeding
- life-threatening and fatal bleeding
- bleeding requiring transfusion

MONITORING

There is no specific lab parameter to indicate the extent of antiplatelet activity.
Monitor for signs and symptoms of bleeding such as:

- unexpected bruising

- frequent and prolonged nosebleeds
- prolonged bleeding following injury
- severe headaches
- melena
- hematuria

PREPARATION FOR SURGICAL PROCEDURES, INCLUDING CABG

Excess bleeding risk due to recent administration of prasugrel in patients selected to have CABG should be weighed against the potential lost benefit of adequate platelet inhibition in early ACS. In patients who may require urgent CABG or urgent non-cardiac surgery, consider discontinuation with the knowledge that platelet function will recover in 7-10 days.

MANAGEMENT OF BLEEDING

Due to the irreversible antagonism of the $P2Y_{12}$ receptor, recovery of platelet function is slower with prasugrel than with the reversible $P2Y_{12}$ receptor antagonist ticagrelor. Because the drug is irreversibly bound, platelet transfusion may be helpful.

- no antidote exists for reversal of antiplatelet effect
- may consider:
  - transfusion of blood products
  - Haematology consult should be obtained for assistance

REFERENCES

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Prepared by: Sidika Dhalla, BScPhm, PharmD Student - August 2012
Reviewed by: John Janevski, MD, and Michelle Baker, BScPhm, ACPR - October 2012
Approved by: Cardiovascular Subcommittee - November 2012;
Pharmacy & Therapeutics Committee - December 2012

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Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

Due to the rapidly changing nature of cardiovascular treatments and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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