PDL NEW DRUG REVIEW

Proprietary Name: Eliquis®
Common Name: apixaban
PDL Category: Anticoagulants

Comparable Products	Preferred Drug List Status
Pradaxa	Non-Preferred
Warfarin	Preferred
Xarelto	Preferred with Conditions

Summary

Indications and Usage: To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. This is a pregnancy category B medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug-Drug Interactions: Apixaban is a substrate of both CYP3A4 and P-glycoprotein (P-gp). Therefore, it is recommended that the dose of apixaban be reduced to 2.5mg BID if using concomitantly with drugs that are strong dual inhibitors of CYP3A4 and P-gp (eg ketoconazole, itraconazole, ritonavir, or clarithromycin). Moreover, in those already on a 2.5mg BID dose, the concomitant use of strong dual inhibitors of CYP3A4 and P-gp should be avoided.

Concomitant use of strong dual inducers of CYP3A4 and P-gp (eg rifampin, carbamazepine, phenytoin, St Johns wort) with apixaban should be avoided, due to a resultant decreased exposure to apixaban.

Lastly, the concomitant use of antiplatelet drugs, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled study to assess efficacy and safety of apixaban use in those with high-risk post-acute coronary syndrome treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to the high rate of bleeding with apixaban vs placebo.

Dosage Forms: Tablets, film-coated: 2.5mg, 5mg

Recommended Dosage: Take 5mg twice daily; however, the recommended dose is 2.5mg twice daily in those with any 2 of the following: age ≥80 years, body weight ≤60kg, serum creatinine ≥1.5mg/dl.

Dosage adjustments are not required in those with mild hepatic impairment; however, as there is limited experience in those with moderate impairment, dosing recommendations cannot be provided. Use in those with severe impairment is not recommended.

Common Adverse Drug Reactions: *Bleeding was the most common adverse event reported in the ARISTOTLE (warfarin comparator) and AVERROES (Aspirin comparator) study. Results reported are vs warfarin, with the %/year result provided for each product.* The most common adverse events reported with Eliquis® includes major bleeding (2.13% vs 3.09%: p<0.001), gastrointestinal bleeding (0.83% vs 0.93%), intracranial bleeding (0.33% vs 0.82%), intraocular bleeding (0.21% vs 0.14%), fatal bleeding (0.06% vs 0.24%), and clinically relevant non-major bleeding (2.08% vs 3%; p<0.0001).

The most frequently reported reason for discontinuation of treatment in both the ARISTOTLE and AVERROES studies was bleeding-related adverse events, reported by 1.7% of the apixaban group vs 2.5% of the warfarin group (ARISTOTLE study) and by 1.5% (apixaban) vs 1.3% (aspirin) in the EVERROES study.

Other reported adverse events in <1% of subjects included hypersensitivity reactions (eg. skin rash and allergic edema) and syncope.

Contraindications: In those with active pathological bleeding; In those with severe hypersensitivity to apixaban or any component of the compound.

Manufacturer: Co-marketed by Bristol-Myers Squibb and Pfizer Inc.

Analysis: Apixaban, the active ingredient of Eliquis®, is a factor Xa (FXa) Inhibitor that as a result, prolongs clotting tests such as prothrombin time (PT). It is a reversible and selective active site inhibitor of FXa, inhibiting free and clot-bound FXa as well as prothrombinase activity. While apixaban has no direct effect on platelet aggregation, it indirectly inhibits platelet aggregation induced by thrombin. Overall, apixaban decreases thrombin generation and thrombus development.

The efficacy and safety of apixaban (Eliquis®) was assessed in the ARISTOTLE trial, a multinational, double-blind, active-comparator trial comprised of adults with non-valvular atrial fibrillation. Apixaban was compared with warfarin to assess the risk of stroke and non-CNS systemic embolism, with the primary outcome assessing if apixaban was effective (non-inferior to warfarin) for reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism. Superiority was also assessed for the primary outcome, along with major bleeding and death from any cause.

Results suggested that apixaban was superior to warfarin for the primary outcome, attributed primarily to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion (purely ischemic strokes occurred at a similar rates between treatments. Results of the primary outcome was 1.27%/year with apixaban vs 1.60% with warfarin (p=0.01). [IME Comments: While this is statistically significantly different, the calculated NNT is 304, suggesting a small clinical effect.] A significantly lower rate of all-cause death was seen with apixaban vs warfarin (3.52% vs 3.94%; p=0.046). Statistically significant fewer major bleeds was seen with apixaban vs warfarin (see adverse events above). [IMEComments: While there is a statistically significant difference in major bleeds, the calculated NNT is 105.]

A second study, the AVERROES study, included patients with non-valvular AFib who were randomized to apixaban or warfarin to assess if apixaban was superior to aspirin in the primary outcome of prevention of the composite outcome of stroke or systemic embolism. Results suggested that there was a statistically significant difference between treatments, with the rate of stroke or systemic embolism with apixaban being 1.62% as compared with 3.63% with aspirin (p<0.0001). [IMEComments: The calculated NNT is 50]. Additionally, the risk of all-cause death was not statistically different (3.51% apixaban vs 4.42% aspirin; p=0.068).

While the ARISTOTLE and AVERROES studies suggest that apixaban is statistically more effective than warfarin and aspirin, respectively, there were no comparator studies found that comparing apixaban with other new oral anticoagulants (eg Pradaxa® or Xarelto®). Nevertheless, as discussed above, while a statistically significant difference was seen between apixaban and warfarin, the calculated NNT was 304, suggesting a small clinical effect. There is no evidence at this time to support that Apixaban® is more efficacious or safer than the currently available new oral anticoagulants. It is recommended that Eliquis® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Eliquis [package insert]. New York, NY: Bristol-Myers Squibb and Pfizer; 2012.

[2] Granger CB, Alexander JH< McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *NEJM*. 2011; 365(11): 981-92

[3] Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban versus warfarin in patients with atrial fibrillation. *NEJM*. 201; 365(8): 699-708..