Indian Health Service
IHS National Pharmacy and Therapeutics Committee
Newer Anticoagulants
June 2013

Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the Target Specific Oral Anticoagulants (TSOAs) at the May 2013 meeting. The discussion included clinical, utilization and procurement data for this class of medications. This discussion did not lead to a formulary modification; however, it was felt that a formulary brief would be of benefit to IHS providers.

Discussion:
New data has emerged regarding TSOAs and their use in patients for prevention of stroke in atrial fibrillation, prophylaxis for venous thromboembolism, and treatment of venous thromboembolism. These products now provide more options for providers and patients in treating conditions and disease states previously managed only by warfarin or other parenteral anticoagulants. Recommendations from recent guidelines and evidence-based medicine encourage use of these medications, but add that often they should be reserved for patients not well managed on warfarin or not affected by TSOAs limiting factors. Furthermore, IHS clinicians should consider cost effectiveness measures such as number needed to treat and number needed to harm when selecting appropriate anticoagulant therapy. There are no head-to-head studies that show a definitive advantage of one agent over the others; therefore, therapy should be individualized based on disease, treatment/prevention goals, cost, and patient specifics.

Evidence from the ARISTOTLE and AVERROES trials shows apixaban 2.5mg and 5mg twice daily doses to be superior to warfarin and aspirin for the prevention of stroke and systemic embolism in the treatment of non-valvular atrial fibrillation. There were statistically significant reductions with apixaban for major and clinically relevant bleeding from the ARISTOTLE trial. Evidence from the RE-LY trial showed dabigatran 150mg twice daily to be superior to warfarin for the prevention of stroke and systemic embolism in the treatment of non-valvular atrial fibrillation. There were similar rates of major and clinically relevant bleeding for dabigatran and warfarin with a statistically significant increase in GI bleed with dabigatran. Evidence from the ROCKET-AF trial showed rivaroxaban 20mg and 15mg once daily to be non-inferior to warfarin for the prevention of stroke and systemic embolism in the treatment of non-valvular atrial fibrillation. There were similar rates of major and clinically relevant bleeding for rivaroxaban and warfarin with a statistically significant decrease in intracranial hemorrhage and fatal bleeding with rivaroxaban. Evidence from the EINSTEIN-DVT, Extension, and PE trials showed rivaroxaban to be non-inferior to current stand of care for the treatment of DVT/PE. There were similar rates of major and clinically relevant bleeding between the two groups studied. Evidence from the MAGELLAN trial showed rivaroxaban to be non-inferior to current standard of care for thromboprophylaxis in the acutely-ill patient; however, there was a statistically significant increase in rates of bleeding in the rivaroxaban group. RECORD-1, -2, -3, and -4 trials showed statistically significant decreases for rivaroxaban in primary efficacy outcomes when compared to enoxaparin.

Findings:
There is clinical merit to the use of TSOAs in appropriate patients. The NPTC did not feel that this class met criteria for inclusion on the National Core Formulary at this time. However, these agents may be very appropriate for inclusion on local formularies to meet the needs of the patients served. The NPTC will continue to watch the clinical data, utilization, and procurement data for this class for future consideration.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

References:

1. Granger CB, Alexander JH, McMurray JJ, et al, "Apixaban versus Warfarin in Patients With Atrial Fibrillation," *N Engl J Med*, 2011, 365(11):981-92.
2. Connolly SJ, Eikelboom J, Joyner C, et al, "Apixaban in Patients With Atrial Fibrillation," *N Engl J Med*, 2011, 364(9):806-17.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al, "Dabigatran Versus Warfarin in Patients With Atrial Fibrillation," *N Engl J Med*, 2009, 361(12):1139-51.
4. Patel MR, Mahaffey KW, Garg J, et al, "Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation," *N Engl J Med*, 2011, 365(10):883-91.
5. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, et al, "Oral Rivaroxaban for Symptomatic Venous Thromboembolism," *N Engl J Med*, 2010, 363(26):2499-510.
6. EINSTEIN-PE Investigators, "Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism," *New Engl J Med*, 2012, 366(14):1287-97.
7. Cohen AT, Sipro TE, Haskell L, et al, "Rivaroxaban for thromboprophylaxis in acutely ill medical patients," *New Engl J Med,* 2013, 368(6):513-23.