Formulary Review: Pradaxa®
Generic Name: Dabigatran
Manufacturer: Boehringer Ingelheim Pharmaceuticals, Inc.
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Executive Summary

Introduction

Pradaxa is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Pharmacology

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

Pharmacokinetics

Table 1. Pharmacokinetic profile

Absorption (AUC)	N/A
Onset	1-2 hrs
Distribution, $V_{d(ss)}$	50-70 L, Protein binding: 35%
Metabolism	Hydrolysis, glucoronidation to 4 active metabolites
Elimination half-life	12-17 hrs

*Renally excreted; renal adjustment required

Clinical Efficacy

In the multi-center, multinational, randomized, parallel-group RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study (n=18,113; mean age 71.5 years) in patients with non-valvular, persistent, paroxysmal, or permanent atrial fibrillation, dabigatran etexilate mesylate 150 mg twice daily was superior to warfarin for reducing the primary composite endpoint of stroke and systemic embolism.

Adverse Drug Reactions

The most common adverse events were gastrointestinal disturbances including gastritis-like symptoms and dyspepsia, and bleeding (16.6%). The most serious complications were gastrointestinal hemorrhage (6.1%), major bleeding (3.3%), anaphylaxis, and intracranial hemorrhage (both <1%)

Drug Interactions

The concomitant use of Pradaxa with P-glycoprotein inducers (e.g., rifampin and St. John's Wort) reduces exposure to dabigatran and should generally be avoided. Rifampin may decrease AUC of dabigatran by up to 67%. Also, use of anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs may increase the risk for bleeding when used concomitantly with dabigatran.

Dosage and Administration

For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of Pradaxa is 150 mg taken orally, twice daily, with or without food. For patients with CrCl 15-30 mL/min, the recommended dose is 75 mg twice daily. Dosing recommendations for patients with a CrCL <15 mL/min or on dialysis cannot be provided. Safety and efficacy has not been established in pediatric patients.

Summary

Pradaxa is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and the RE-LY study showed Pradaxa to be superior to warfarin for this indication. Serious side effects include gastrointestinal hemorrhage and major bleeding. Pradaxa must be renally adjusted from 150 mg po BID to 75 mg po BID in patients with CrCl 15-30 ml/minute. Pradaxa may be taken without respect to food, and does not require therapeutic blood monitoring. Pradaxa has not been approved by the FDA to treat or prevent venous thromboembolism (DVT or PE).

Status

Formulary; Orders for patients receiving this medication as an outpatient are currently approved for formulary use. ***New starts for this agent require authorization via the non-formulary approval process***.