Rivaroxaban (NDA 22-406)

Clinical Pharmacology

Christoffer W. Tornoe, Ph.D.
Office of Clinical Pharmacology
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Bottom Line Up Front

• Is there Evidence of Dose/Exposure-Response for Effectiveness and Safety?
  – Shallow dose-response
  – Increased bleeding risk with increasing rivaroxaban dose/exposure

• Which Special Populations are at Risk for Clinically Relevant Increases in Exposure?
  – Moderate-severe hepatic patients
  – Use of strong CYP3A4/P-gp inhibitors
  – Mild-moderate renal impairment + moderate CYP3A4/P-gp inhibitors

• What are the Strategies to Address Increased Exposure and Risk of Bleeding in Special Populations?
  – Lower dose strengths is the best option and will allow a larger patient population to receive this treatment
Pharmacokinetic Characteristics

• Absorption ~ 100%

• $T_{1/2} \sim 5$-9 hours in healthy subjects

• Metabolism
  – ~50% of an orally administered dose undergoes metabolic degradation predominantly by CYP3A4/5

• Excretion
  – 50% excreted unchanged via P-gp/BCRP mediated active renal secretion (~36%) and in the feces (~7%).
Key Questions

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Shallow Dose-Response Relationship for Composite Efficacy Endpoint

*The error bars represent the 95% confidence interval of the mean proportions*
Increasing Risk of Major Bleeding with Increasing Dose and Exposure

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Moderate Hepatic Impairment and Strong CYP3A4/P-gp Inhibitors have >2-fold Increase in Exposure

Renal Impairment
- Severe (<30 mL/min): 1.6
- Moderate (30—50 mL/min): 1.5
- Mild (50-80 mL/min): 1.4

Hepatic Impairment
- Child-Pugh B: 2.3
- Child-Pugh A: 1.2

Drug Interactions
- Ritonavir: 2.5
- Ketoconazole: 2.6
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Availability of 5 mg Tablet Enables Matching Exposure and Risk of Major Bleeding in Special Populations

The chart illustrates the relationship between Steady-state AUC (mg*hr/L) and the risk of major bleeding (%). It shows that the availability of 5 mg tablets enables matching exposure and risk in special populations. The diagram includes different dosage levels and hepatic impairment scenarios.
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