Ximelagatran
Clinical Pharmacology

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Ximelagatran—An Oral Direct Thrombin Inhibitor

Bioconversion CYP450 independent

80% renally excreted
Direct Thrombin Inhibition

- Thrombin—a key enzyme
- Melagatran directly inhibits thrombin
  - Competitive and reversible-binding inhibitor
  - Direct PK/PD relationship
  - Antithrombotic effects in animals begin at 0.05 µmol/L
Concentration-Dependent Prolongation of the Thrombin Time in Humans by Melagatran

Melagatran plasma concentration, µmol/L

Thrombin time, s

$R^2 = 0.96$

~0.05 µmol/L
Concentration-Dependent Prolongation of the APTT in Humans by Melagatran

Predose APTT values not included in regression. Ximelagatran doses of 5 to 98 mg.
Ximelagatran—Pharmacologic Activity in Humans

Concentration-dependent reductions in a human shed blood model

Ximelagatran doses of 15 to 60 mg.
Ximelagatran—Rapid Onset of Action

Atrial fibrillation patients; n = 12.

Oral ximelagatran 36 mg

Plasma concentrations, µmol/L

Time, hr

0 1 2 3 4 5 6 7 8 9 10 11 12

0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50

0.05 µmol/L

Ximelagatran—Rapid Onset of Action
Ximelagatran—No Food Interaction

Oral ximelagatran 36 mg

Young healthy subjects; n = 50.
Ximelagatran—Drug Interaction Investigations

- No metabolism by or inhibition of P450 isoenzymes
  - CYPs 1A2, 2C9, 2C19, 2D6, 2E1, 3A4

- Melagatran has low (<15%) plasma protein binding
**Ximelagatran—Drug Interaction Investigations**

† Melagatran AUC ratio – ximelagatran + comedication vs ximelagatran alone.

<table>
<thead>
<tr>
<th>Comedication</th>
<th>Melagatran AUC ratio†</th>
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<tbody>
<tr>
<td>Erythromycin 500 mg</td>
<td>2.0</td>
</tr>
<tr>
<td>Azithromycin 500 mg</td>
<td>1.5</td>
</tr>
<tr>
<td>Azithromycin 250 mg</td>
<td>1.0</td>
</tr>
</tbody>
</table>

† Geometric mean ratio (90% CI)

No interaction interval
Ximelagatran—Drug Interaction Investigations

† Geometric mean ratio (90%CI); ximelagatran 24 or 36 mg. Melagatran AUC ratio – ximelagatran + comedication vs ximelagatran alone.
Dose normalized to 36 mg BID.
Population model predicted steady-state melagatran AUC (µmol·h/L).
Ximelagatran Pharmacokinetics in Special Patient Populations

- Renal function influences melagatran exposure
- No other important effects of
  - Age
  - Gender
  - Race
  - BMI
  - Body weight
Ximelagatran—Dosing in Renally Impaired Patients

- No need for dose-adjustment in TKR patients
- No increase in bleeding related to melagatran exposure in VTE secondary prevention patients
- Association between increasing melagatran exposure and major bleeding in atrial fibrillation patients
  - Confounded by changes in calculated CrCL
Relationship of Calculated CrCL With Major Bleeding
SPORTIF III / SPORTIF V

Proportion of major bleeding in SPORTIF III/V by CrCL.

- Warfarin major bleeding
- Ximelagatran major bleeding

Patients with major bleeding, %

Calculated CrCL, mL/min

Proportion of major bleeding in SPORTIF III/V by CrCL.
Proportion of stroke/SEE in SPORTIF III/V by CrCL; SEE = Systemic embolic event.
Melagatran AUC vs Peak ALT Elevation

$R^2 = 0.002$

$p = 0.0003$
Fixed Dosing With Oral Ximelagatran

Ximelagatran fixed dosing

- Total knee replacement
- 2° prevention of VTE
- Stroke/SEE prevention in atrial fibrillation
Steady-State Melagatran Concentrations and APTT Prolongations in AF Patients

Ximelagatran 36 mg twice-daily; n = 49; mean ± SD.
Ximelagatran Pharmacokinetics in AF Patients

~13 - 16 mo between sampling times

Total variability ~50% (CV%); intrapatient variability ~25%.
Dose normalized to 36 mg ximelagatran twice daily.
Clinical Pharmacology Conclusions

- Pharmacologically active concentrations of melagatran are rapidly achieved and maintained in a broad range of patients
- No effect of food or alcohol
- Low potential for drug interactions
- A fixed dose without coagulation monitoring