Abstract: P1706

**Metabolism and pharmacokinetic drug interaction profile of vericiguat, a soluble guanylate cyclase stimulator**

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**Topic(s):**
Chronic Heart Failure: Pharmacotherapy

**Citation:**

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Background/Introduction: Vericiguat is under investigation in patients with heart failure (HF; NCT02861534). This patient population is characterised by multiple comorbidities and concomitant medications.

Purpose: An understanding of the clearance mechanisms, elimination and potential for drug–drug interactions (DDIs) of vericiguat is a pre-requisite for dose recommendations.

Methods: Biotransformation of vericiguat was characterised in vitro using hepatocytes, liver microsomes, recombinant uridine diphosphate-glucuronosyltransferase (UGT) isoforms and with selective UGT inhibitors in liver microsomes. These were complemented by a human mass balance study with a single dose of 14C-labelled vericiguat 5 mg and six DDI studies in healthy volunteers (Table 1). The perpetrator DDI potential of vericiguat was investigated in vitro.

Clinically, the perpetrator DDI potential was assessed with the narrow-therapeutic index drugs digoxin and warfarin, and the cytochrome P450 (CYP) 3A4 index substrate midazolam. Vericiguat was administered as a victim drug with ketoconazole, rifampicin and mefenamic acid.

Results: After administration of 14C-labelled vericiguat, 53.1% and 45.2% of the dose was excreted via urine and faeces, respectively. The main metabolic pathway of vericiguat is glucuronidation via UGT1A9 and UGT1A1.

In vitro studies revealed that the risk of pharmacokinetic (PK) DDIs with substrates of CYP and UGT isoforms, as well as major transport proteins, is low. These were confirmed by the clinical studies (Figure 1).

Conclusion(s): A low PK interaction potential of vericiguat was estimated from in vitro data and confirmed in six studies. Maximum changes in vericiguat exposure (~30%) were within the range of overall PK vericiguat variability. These results indicate that the PK DDI profile of vericiguat is suited to the treatment of a HF population.

| Table 1 |  |
| --- | --- | --- |
| Healthy volunteer study | Design | Vericiguat treatment | Co-medication |
| Mass balance | Open-label, non-randomised, | 5 mg | Not applicable |
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<table>
<thead>
<tr>
<th>DDI with perpetrator</th>
<th>Study design</th>
<th>Vericiguat treatment</th>
<th>Co-medication</th>
<th>Clinical comment</th>
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<tbody>
<tr>
<td>warfarin</td>
<td>Randomised, double-blind, 2-fold crossover</td>
<td>10 mg OD for 9 days</td>
<td>Warfarin 25 mg SD</td>
<td>No dose adjustment of warfarin</td>
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<tr>
<td>digoxin</td>
<td>Randomised, open-label, 2-fold crossover with additional fixed treatment period</td>
<td>10 mg OD for 10 days; 10 mg SD</td>
<td>Digoxin 0.375 mg OD for 14 days</td>
<td>No dose adjustment of digoxin</td>
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<tr>
<td>CYP3A4 index substrate</td>
<td>Randomised, open-label, 2-fold crossover</td>
<td>10 mg OD for 4 days</td>
<td>Midazolam 7.5 mg SD</td>
<td>No dose adjustment of co-medications metabolised by CYP3A4</td>
</tr>
<tr>
<td>multi-pathway inhibitor</td>
<td>Randomised, open-label, 2-fold crossover</td>
<td>1.25 mg SD</td>
<td>Pre- and co-administration of ketoconazole 200 mg BID for 3 days</td>
<td>No dose adjustment of vericiguat</td>
</tr>
<tr>
<td>multi-pathway inducer</td>
<td>Randomised, open-label, fixed sequence</td>
<td>10 mg SD</td>
<td>Pre- and co-administration of rifampicin 600 mg OD for 9 days</td>
<td>No dose adjustment of vericiguat</td>
</tr>
<tr>
<td>UGT1A9 inhibitor</td>
<td>Randomised, open-label, 2-fold crossover</td>
<td>2.5 mg SD</td>
<td>Pre- and co-administration of mefenamic acid 500 mg followed by MDs of mefenamic acid 250 mg every 6 hours for 3 days</td>
<td>No dose adjustment of vericiguat</td>
</tr>
</tbody>
</table>

BID, twice-daily; CYP, cytochrome P450; DDI, drug–drug interaction; MD, multiple dose; OD, once-daily; SD, single dose; UGT, uridine diphosphate-glucuronosyltransferase