Micafungin (mycamine®) is a semi-synthetic antifungal drug belonging to the novel echinocandin class. As its absorption is very poor, micafungin is only available as an intravenous (iv) formulation.

**BACKGROUND**

Micafungin is not extensively metabolised and renal clearance does not constitute a major pathway (Figure 2). Hepatobiliary clearance seems to be the main route of elimination for this compound — indicating a key role of transporters in its disposition — with hepatic uptake occurring primarily via NTCP and to a lesser extent via OATP(s) and biliary excretion occurring primarily via BSEP.

**OBJECTIVE**

To develop a preliminary physiologically-based pharmacokinetic (PBPK) model, to be used in the prediction of micafungin disposition in different populations.

**METHODS**

Physicochemical information and in vitro/in vivo data on the clearance of micafungin were used in a full PBPK model, implemented in the Simcyp Population-based Simulator (V132), as follows:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Model I Top-down</th>
<th>Model II Retrograde</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Vm prediction - Method 2: Rodgers &amp; Roland, using:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- hepatic uptake scalar of 1.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vm prediction - Method 2: Rodgers &amp; Roland, using:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- hepatic uptake scalar of 1.6</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>CLh (in vivo)</td>
<td>CLh (in vivo)</td>
</tr>
<tr>
<td>Clearance</td>
<td>CLr (in vivo)</td>
<td>CLr (in vivo)</td>
</tr>
</tbody>
</table>

Concentration-time profiles of micafungin were simulated in healthy volunteers (HVs) following 100 mg single-dose (SD) iv administration to assess pharmacokinetic parameters compared to observed data.

As additional validation of the model, concentration-time profiles were simulated in:

- Simcyp Japanese population at doses of 50, 75, and 150 mg - pharmacokinetic profile was compared to observed data.

- Simcyp renal-impaired population (GFR < 30 mL/min) at a dose of 100 mg - pharmacokinetic profile was compared to observed data.

**RESULTS**

**PBPK Model I Simcyp-Healthy Volunteer**

The simulated concentration-time profile of micafungin (100 mg – iv) indicated no effect of renal impairment on micafungin PK parameters, which is consistent with findings that CL(Renal) is a minor elimination pathway.

**PBPK Model II Retrograde Clearance Breakdown**

To further develop this PBPK model, in vivo clearance was divided into the separate pathways involved in micafungin clearance:

**REFERENCES**


Simulations were carried out in 250 male-only subjects (10 trials x 25 subjects). Age-range: 20-31 years. Average weight: 66 kg. Red circles represent the observed mean values from the respective clinical study of micafungin.