COVID-19 Antiviral Therapies (Licensed or Under Clinical Investigation)

Please refer to the additional notes on the following pages for further details and complete dose recommendations.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mild (Childs Pugh A)</th>
<th>Moderate (Childs Pugh B)</th>
<th>Severe (Childs Pugh C)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>100%</td>
<td>100%</td>
<td>Not recommended</td>
<td>1, 2</td>
</tr>
<tr>
<td>Bamlanivimab/ Etesevimab</td>
<td>100%</td>
<td>100% (no data available)</td>
<td>100% (no data available)</td>
<td>3</td>
</tr>
<tr>
<td>Casirivimab/ Imdevimab</td>
<td>100%</td>
<td>100% (limited data available)</td>
<td>100% (no data available)</td>
<td>4, 5</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Consider dose adjustment. 1200 mg twice daily then 800 mg twice daily to day 5</td>
<td>Consider dose adjustment. 1200 mg twice daily then 800 mg twice daily to day 5</td>
<td>Consider dose adjustment. 800 mg twice daily then 400 mg twice daily to days 2-3</td>
<td>6, 7</td>
</tr>
<tr>
<td>Molnupiravir</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>8, 9</td>
</tr>
<tr>
<td>Niclosamide</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>10</td>
</tr>
<tr>
<td>Nirmatrelvir + ritonavir</td>
<td>100%</td>
<td>100%</td>
<td>Contraindicated</td>
<td>11, 12</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>100%, with caution. Not studied in hepatic disease.</td>
<td>100%, with caution. Not studied in hepatic disease.</td>
<td>100%, with caution. Not studied in hepatic disease.</td>
<td>13</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>100% (no data available)</td>
<td>100% (no data available)</td>
<td>100% (no data available)</td>
<td>14, 15</td>
</tr>
<tr>
<td>Sotrovimab</td>
<td>100% (no data available)</td>
<td>100% (no data available)</td>
<td>100% (no data available)</td>
<td>16, 17</td>
</tr>
<tr>
<td>Tixagevimab/Cilgavimab</td>
<td>100% (no data available)</td>
<td>100% (no data available)</td>
<td>100% (no data available)</td>
<td>18</td>
</tr>
</tbody>
</table>
Azithromycin  
Hepatic elimination: use with caution in all degrees of hepatic impairment. Discontinue if signs of hepatic dysfunction.

Bamlanivimab/ Etesevimab  
No dosage adjustment is recommended in patients with mild hepatic impairment. Based on population PK analysis, there is no difference in PK of bamlanivimab or etesevimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bamlanivimab and etesevimab have not been studied in patients with moderate or severe hepatic impairment.

Casirivimab/ Imdevimab  
Casirivimab and imdevimab are not expected to undergo significant hepatic elimination. No dosage adjustment is required in individuals with mild hepatic impairment. The effect of hepatic impairment on the exposure of casirivimab and imdevimab was evaluated by population PK analysis in patients with mild hepatic impairment (n=586 for casirivimab; n=599 for imdevimab) (total bilirubin >1.0-1.5 x ULN and any aspartate aminotransferase). No clinically important differences in the exposure of casirivimab and imdevimab were found between patients with mild hepatic impairment and patients with normal hepatic function. Limited data (n=11) are available in patients with moderate hepatic impairment; no data are available in patients with severe hepatic impairment.

Favipiravir  
Could consider extending treatment duration in COVID as per duration for ongoing trials. Dosing as per study US109.

Molnupiravir  
No dose adjustment is required for patients with hepatic impairment. The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore hepatic impairment is unlikely to affect NHC exposure.

Niclosamide  
Niclosamide may be given safely to patients with liver diseases.

Nirmatrelvir + ritonavir  
Nirmatrelvir and ritonavir exposures were similar in subjects with normal hepatic function and those with moderate hepatic impairment. No dosage adjustment is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

Nirmatrelvir/ritonavir is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) as it has not been studied and there are no pharmacokinetic or safety data available regarding its use in subjects with severe hepatic impairment.

Nitazoxanide  
The pharmacokinetics of nitazoxanide in patients with compromised hepatic function have not been studied.

Remdesivir  
The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. The role of the liver in the metabolism of remdesivir is unknown. It is not known if dosage adjustment is appropriate in patients with hepatic impairment. Remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Liver function should be determined in all patients prior to starting remdesivir and should be monitored while receiving it as clinically appropriate.

The SmPC recommends that remdesivir should not be initiated in patients with ALT ≥5x ULN at baseline. Remdesivir should be discontinued in patients who develop ALT ≥5x ULN (SmPC) or >10x ULN (USPI) during treatment with remdesivir.

Remdesivir should be discontinued in patients who develop ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

Sotrovimab  
No clinical trials have been conducted to evaluate the effects of hepatic impairment on the pharmacokinetics of sotrovimab.

The impact of hepatic impairment on sotrovimab is unknown.

Tixagevimab/ Cilgavimab  
No specific studies have been conducted to examine the effects of hepatic impairment on the pharmacokinetics of tixagevimab and cilgavimab.

The effect of hepatic impairment on the pharmacokinetics of tixagevimab and cilgavimab is unknown.
**COVID-19 Host-directed Therapies (Licensed or Under Clinical Investigation)**

*Please refer to the additional notes on the following pages for further details and complete dose recommendations.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hepatic Impairment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anakinra</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>19, 20</td>
</tr>
<tr>
<td>100%</td>
<td>100%, with caution</td>
<td></td>
</tr>
<tr>
<td><strong>Baricitinib</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>21, 22</td>
</tr>
<tr>
<td><strong>Budesonide</strong> (inhaled)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not studied. Consider 100% with close monitoring.</td>
<td>Not studied. Consider 100% with close monitoring.</td>
<td>23, 24</td>
</tr>
<tr>
<td><strong>Canakinumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>25, 26</td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dexamethasone</strong> (low dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>27, 28</td>
</tr>
<tr>
<td>100%</td>
<td>100%, with caution</td>
<td></td>
</tr>
<tr>
<td><strong>Fluvoxamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% following slow titration and careful monitoring</td>
<td>100% following slow titration and careful monitoring</td>
<td>29, 30</td>
</tr>
<tr>
<td><strong>Hydrocortisone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not studied. Consider dose reduction.</td>
<td>Not studied. Consider dose reduction.</td>
<td>31</td>
</tr>
<tr>
<td><strong>Infliximab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not studied. No dosing recommendations can be made.</td>
<td>Not studied. No dosing recommendations can be made.</td>
<td>32, 33</td>
</tr>
<tr>
<td><strong>Methylprednisolone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not studied. Consider 100%.</td>
<td>Not studied. Consider 100%.</td>
<td>34, 35</td>
</tr>
<tr>
<td><strong>Ruxolitinib</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% (dosing as per platelet count in product label)</td>
<td>50% (dosing as per platelet count in product label)</td>
<td>36-38</td>
</tr>
<tr>
<td><strong>Sarilumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not studied. Consider 100% under specialist supervision with frequent ALT monitoring.</td>
<td>Not studied. Consider 100% under specialist supervision with frequent ALT monitoring.</td>
<td>39</td>
</tr>
<tr>
<td><strong>Tocilizumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not studied. Consider 100% under specialist supervision with frequent ALT monitoring.</td>
<td>Not studied. Consider 100% under specialist supervision with frequent ALT monitoring.</td>
<td>40, 41</td>
</tr>
</tbody>
</table>
Notes - Host-directed Therapies (Licensed or Under Clinical Investigation)

Anakinra
The efficacy and safety in patients with AST/ALT ≥1.5x ULN have not been evaluated.

Baricitinib
There was no clinically relevant effect on the pharmacokinetics of baricitinib in patients with mild or moderate hepatic impairment. The use of baricitinib has not been studied in patients with severe hepatic impairment.

Budesonide
Formal pharmacokinetic studies with inhaled budesonide have not been conducted in patients with hepatic impairment. However, since budesonide undergoes mainly hepatic metabolism, impairment of liver function may lead to accumulation of budesonide in the plasma. Patients with hepatic disease should be closely monitored.

Canakinumab
No formal pharmacokinetic studies have been performed in patients with hepatic impairment. Elimination of protein drugs such as canakinumab is thought to occur via proteolytic catabolism in different tissues. Although the liver is known to be a major organ of protein degradation, impaired hepatic function is not expected to be a limiting factor for elimination.

Colchicine
Use with caution in patients with mild/moderate hepatic impairment. Such patients should be carefully monitored for adverse effects of colchicine. Coadministration is contraindicated in the SmPC for patients with severe hepatic impairment, but the USPI recommends to consider dose reduction. Coadministration is contraindicated in patients with hepatic impairment who are taking a P-gp inhibitor or a strong CYP3A4 inhibitor.

Fluvoxamine
Fluvoxamine undergoes extensive hepatic metabolism. In patients with liver cirrhosis, fluvoxamine AUC increased by ~56% when compared to healthy volunteers.

Dexamethasone
Particular care is required when considering the use of systemic corticosteroids in patients with liver failure and frequent patient monitoring is necessary. The elimination half-life is prolonged in severe liver disease.

Hydrocortisone
There may be an increased effect in patients with liver disease, and monitoring is advised. Reduced dosing may be considered.

Methylprednisolone
Particular care is required when considering the use of systemic corticosteroids in patients with liver failure or cirrhosis and frequent patient monitoring is necessary.

Ruxolitinib
Recommendations as for polycythaemia vera indication in product labels.

Sarilumab
Initiating treatment is not recommended in patients with ALT or AST >1.5x ULN.

Tocilizumab
The European product label does not recommend treatment in patients with baseline ALT or AST >5x ULN. The American product label does not recommend to initiate treatment in patients with elevated transaminases ALT or AST >1.5x ULN.
Antiviral Therapies
1. Zithromax (azithromycin) Summary of Product Characteristics, Pfizer Ltd.
2. Zithromax (azithromycin) Prescribing Information, Pfizer Inc.
3. Bamlanivimab and etesevimab FDA Emergency Use Authorization, Lilly USA.
4. Ronapreve (casirivimab/imdevimab) Summary of Product Characteristics, Roche Products Ltd.
5. REGEN-COV (casirivimab/imdevimab) FDA Emergency Use Authorization, Regeneron Pharmaceuticals Inc.
6. Avigan (favipiravir) Japanese Product Label, Toyama Chemical Co Ltd.
7. Pharmacokinetics of favipiravir in volunteers with hepatic impairment. ClinicalTrials.gov Identifier: NCT01419457.
8. Lagevrio (molnupiravir) Summary of Product Characteristics, Merck Sharp and Dohme Ltd.
10. Yomesan (niclosamide) Prescribing Information, Bayer (discontinued).
11. Paxlovid (nirmatrelvir/ritonavir) Summary of Product Characteristics, Pfizer Ltd.
15. Veklury (remdesivir) US Prescribing Information, Gilead Sciences Inc.
22. Olumiant (baricitinib) US Prescribing Information, Lilly USA.
25. Ilaris (canakinumab) US Prescribing Information, Novartis Pharmaceuticals.
29. Faverin (fluvoxamine) Summary of Product Characteristics, Mylan.
30. Luvox (fluvoxamine) US Prescribing Information, ANI Pharmaceuticals Inc.
31. Solu-Cortef (hydrocortisone) Summary of Product Characteristics, Pfizer Ltd.
32. Remicade (infliximab) Summary of Product Characteristics, Merck Sharp and Dohme Ltd.
34. Medrone (methylprednisolone) Summary of Product Characteristics, Pfizer Ltd.
35. Medrol (methylprednisolone) US Prescribing Information, Pfizer.
36. Jakavi (ruxolitinib) Summary of Product Characteristics, Novartis Pharmaceuticals Ltd.
40. RoActemra (tocilizumab, for infusion) Summary of Product Characteristics, Roche Products Ltd.
41. Actemra (tocilizumab) US Prescribing Information, Genentech Inc.

References

Host-directed Therapies
22. Olumiant (baricitinib) US Prescribing Information, Lilly USA.
25. Ilaris (canakinumab) US Prescribing Information, Novartis Pharmaceuticals.
29. Faverin (fluvoxamine) Summary of Product Characteristics, Mylan.
30. Luvox (fluvoxamine) US Prescribing Information, ANI Pharmaceuticals Inc.
31. Solu-Cortef (hydrocortisone) Summary of Product Characteristics, Pfizer Ltd.
32. Remicade (infliximab) Summary of Product Characteristics, Merck Sharp and Dohme Ltd.
34. Medrone (methylprednisolone) Summary of Product Characteristics, Pfizer Ltd.
35. Medrol (methylprednisolone) US Prescribing Information, Pfizer.
36. Jakavi (ruxolitinib) Summary of Product Characteristics, Novartis Pharmaceuticals Ltd.
40. RoActemra (tocilizumab, for infusion) Summary of Product Characteristics, Roche Products Ltd.
41. Actemra (tocilizumab) US Prescribing Information, Genentech Inc.