Evaluating the drug-drug interaction risk of experimental COVID-19 therapies

How we make our evaluations

The scale in use of experimental therapies for COVID-19 is unprecedented. Accepting that evidence of benefit remains to be established for these agents, we have sought to make our drug-drug interaction (DDI) recommendations evidence-based, pragmatic and clinically useful. This has meant that, in addition to our usual criteria (Seden et al, 2017), we have also taken into account:

- the likely critical condition of any patient requiring these therapies
- the relatively short duration of co-administration
- the incremental risks to health workers from additional monitoring
- the available, safer alternatives
- the option of pausing the co-medications whilst COVID therapy is administered

We always strive to make recommendations based on knowledge and evidence, and to be transparent and accountable. Some COVID therapies have few published data, so we have resorted to using what we can get hold of. Therefore, the quality of evidence for all unpublished data should be regarded as very low.

In the sections below, we have summarised our understanding of the pharmacology of experimental therapies, and the basis on which our DDI evaluations have been made. In addition, the CredibleMeds.org website was used to identify drugs with known, possible or conditional risks of QT prolongation and/or TdP. The risk may be increased when combining drugs as a result of pharmacodynamic (additive effect) and/or pharmacokinetic (increase in exposure) DDIs.

The decision to give or withhold drugs is always the responsibility of the prescriber. A pragmatic use of our DDI recommendations is to regard Green and Yellow flags on the interaction checker as an indication that no clinically significant DDIs exist, while Red flags indicate significant cause for concern. An Amber flag does not preclude co-administration (since DDIs are usually manageable), but rather indicates the need to consider risks and benefits in that individual patient for whom treatment is considered.

Please note that for drugs also listed on our HIV and HEP websites, interactions when used for COVID may be different due to the short duration of treatment.

Details of the metabolism, interaction potential and cardiac effects are available for the following experimental COVID therapies:

- Anakinra
- Atazanavir
- Azithromycin
- Bamlanivimab / Etesevimab
- Baricitinib
- Budesonide (inhaled)
- Canakinumab
- Casirivimab / Imdevimab
- Chloroquine
- Colchicine
- Dexamethasone
- Favipiravir
- Hydrocortisone (oral or IV)
- Hydroxychloroquine
- Infliximab
- Interferon beta
- Ivermectin
- Lopinavir/ritonavir
- Methylprednisolone (oral or IV)
- Molnupiravir
- Niclosamide
- Nitazoxanide
- Remdesivir
- Ribavirin
- Ruxolitinib
- Sarilumab
- Sotrovimab
- Tocilizumab
**Anakinra**

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Anakinra is recombinant human interleukin-1 (IL-1) receptor antagonist and is eliminated by glomerular filtration and subsequent tubular metabolism.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Anakinra, per se, has no inhibitory or inducing effects on cytochromes. However, anakinra reverses IL-1 induced suppression of cytochromes (elevation of IL-1 during inflammation has been shown to inhibit CYP3A4, CYP2C19, CYP2C9 and CYP1A2 expression/activity resulting in higher drug exposure of substrate drugs). Upon treatment with anakinra, cytochrome activity normalizes leading to reduced exposure of drugs which, prior to treatment with anakinra, had been adjusted to the metabolism of individuals with rheumatoid arthritis.  
• Patients infected with COVID19 experience an elevation of IL-1. However, since comedinations will not have been adjusted to the acute inflammatory COVID19 state and since treatment with anakinra is initiated rapidly, no a priori adjustment of CYP3A4, CYP2C19, CYP2C9, CYP1A2 substrates is needed. The effect of acute COVID infection on drugs with a narrow therapeutic index is unclear.  
• Caution is required when coadministering with myelotoxic drugs due to the potential additive haematological toxicity.  
• Coadministration with monoclonal antibodies should be avoided due to the enhanced immunosuppressive effect. |

**Cardiac effects**

There were no significant changes in QT intervals in animals treated with anakinra alone at 100 mg/kg or in combination with PEG sTNF-RI (pegylated inhibitor of the TNF receptor) at doses up to 25 mg/kg.

**References**

- Kineret Summary of Product Characteristics, Swedish Orphan Biovitrum.
- Kineret US Prescribing Information, Swedish Orphan Biovitrum.
- Kineret EPAR Scientific Discussion, European Medicines Agency.

---

**Atazanavir**

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Atazanavir is principally metabolised by CYP3A4. Metabolites are excreted in the bile as either free or glucuronidated metabolites. After multiple dosing, mean urinary excretion of unchanged drug was 7%.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Atazanavir is an inhibitor of CYP3A4 and UGT1A1, and a strong inhibitor of OATP1B1. Coadministration of atazanavir and drugs primarily metabolized by CYP3A or UGT1A1, or transported by OATP1B1, may increase plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects.  
• Atazanavir is a weak inhibitor of CYP2C8. Use of atazanavir (without ritonavir) is not recommended when coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices.  
• Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected with proton-pump inhibitors, antacids, buffered medications, and H2-receptor antagonists. |

**Cardiac effects**

Dose related asymptomatic prolongations in the PR interval with atazanavir have been observed in clinical studies. Caution should be used when prescribing atazanavir with medicinal products which have the potential to increase the QT interval and/or in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances).

**References**

- Reyataz Summary of Product Characteristics, Bristol-Myers Squibb.
- Reyataz US Prescribing Information, Bristol-Myers Squibb.
## Azithromycin

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Azithromycin is extensively metabolised and is mainly eliminated via biliary excretion with animal data suggesting that this may occur via P-gp and MRP2.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Azithromycin does not interact significantly with the hepatic cytochrome P450 system. Hepatic cytochrome P450 induction or inactivation does not occur with azithromycin.  
• Azithromycin may inhibit P-gp but the clinical significance of this is unclear. |
| Cardiac effects | Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with azithromycin. Cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving azithromycin. In a study in healthy subjects, coadministration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. |

### References
- Zithromax Summary of Product Characteristics, Bristol-Myers Squibb.
- Zithromax US Prescribing Information, Bristol-Myers Squibb.

## Bamlanivimab / Etesevimab

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Bamlanivimab and etesevimab are IgG1 monoclonal antibodies and are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Bamlanivimab and etesevimab are not metabolized by cytochrome P450 enzymes.  
• Interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.  
• It is possible that bamlanivimab and etesevimab may interfere with the development of effective immune responses to COVID-19 vaccines. Refer to current vaccination guidelines with respect to timing of vaccination post treatment with anti-SARS-CoV-2 monoclonal antibodies. |
| Cardiac effects | The QT interval prolongation risks for bamlanivimab and etesevimab have not been assessed but are considered to be low. |
| References | Bamlanivimab and etesevimab FDA Emergency Use Authorization, Lilly USA. |
### Baricitinib

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Baricitinib metabolism is mediated by CYP3A4, with &lt;10 % of the dose identified as undergoing biotransformation. Renal elimination is the principal mechanism for baricitinib's clearance through glomerular filtration and active secretion via OAT3, P-gp, BCRP and MATE2-K.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Baricitinib may be a clinically relevant inhibitor of the transporter OCT1, but it does not inhibit OAT1, OAT2, OAT3, OCT2, OATP1B1, OATP1B3, BCRP, MATE1 and MATE2-K at clinically relevant concentrations.  
• In vitro, baricitinib did not significantly inhibit or induce the activity of cytochrome P450 enzymes (CYPs 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6).  
• In clinically pharmacology studies, baricitinib had no clinically meaningful effect on the pharmacokinetics of the CYP3A substrates simvastatin, ethinylestradiol or levonorgestrel.  
• There is a risk of additional immunosuppression when baricitinib is coadministered with other immunosuppressants. Coadministration with biological disease-modifying anti-rheumatic drugs or Janus kinase inhibitors is not recommended. |
| Cardiac effects | At a dose 10 times the maximum recommended dose, baricitinib does not prolong the QT interval to any clinically relevant extent. |
| References | Olumiant Summary of Product Characteristics, Lilly.  
Olumiant US Prescribing Information, Lilly. |

### Budesonide (inhaled)

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Budesonide is a CYP3A4 substrate.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Budesonide does not inhibit or induce CYPs.  
• Increased concentrations of budesonide as a result of CYP3A4 inhibition are unlikely to be clinically significant given the short duration of inhaled budesonide used in COVID-19 treatment (2 weeks). However, prescribers should be aware of and to look out for signs of systemic corticosteroid side effects. |
| Cardiac effects | No clinically significant effect on QTc was observed in 14 patients receiving high dose budesonide/formoterol treatment. |
| References | Pulmicort Summary of Product Characteristics, Astra Zeneca.  
Pulmicort US Prescribing Information, Astra Zeneca.  
**Canakinumab**

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Canakinumab is a recombinant human interleukin-1 (IL-1) receptor antagonist and is eliminated via intracellular catabolism.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Canakinumab, per se, has no inhibitory or inducing effects on cytochromes. However, canakinumab reverses IL-1 induced suppression of cytochromes (elevation of IL-1 during inflammation has been shown to inhibit CYP3A4, CYP2C19, CYP2C9 and CYP1A2 expression/activity resulting in higher drug exposure of substrate drugs). Upon treatment with canakinumab, cytochrome activity normalizes leading to reduced exposure of drugs which, prior to treatment with canakinumab, had been adjusted to the metabolism of individuals with various inflammatory conditions.  
  • Patients infected with COVID19 experience an elevation of IL-1. However, since concomitant medications will not have been adjusted to the acute inflammatory COVID19 state and since treatment with canakinumab is initiated rapidly, no a priori adjustment of CYP3A4, CYP2C19, CYP2C9, CYP1A2 substrates is needed. The effect of acute COVID infection on drugs with a narrow therapeutic index is unclear.  
  • Caution is required when co-administering with myelotoxic drugs due to the potential additive haematological toxicity.  
  • Co-administration with monoclonal antibodies should be avoided due to the enhanced immunosuppressive effect.  
  • Use of canakinumab with TNF inhibitors is not recommended as this may increase the risk of serious infections. An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. |

**Cardiac effects**

The QT interval prolongation risk of canakinumab is considered to be low. Stand-alone safety pharmacology studies were not conducted with canakinumab. However, the cardiovascular system was analysed as part of toxicology studies. No treatment-related effects on electrocardiography data were observed throughout treatment and recovery periods.

**References**

Ilaris Summary of Product Characteristics, Novartis Pharmaceuticals.
Ilaris US Prescribing Information, Novartis Pharmaceuticals.
Ilaris CHMP Assessment Report, European Medicines Agency.

**Casirivimab / Imdevimab**

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Casirivimab and imdevimab are IgG1 monoclonal antibodies and are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Casirivimab and imdevimab are not metabolized by cytochrome P450 enzymes.  
  • Interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.  
  • Casirivimab and imdevimab bind to epitopes on spike protein used as immunogen in all COVID-19 vaccines, therefore it is possible that casirivimab and imdevimab may interfere with the development of effective immune responses to COVID-19 vaccines. Refer to current vaccination guidelines with respect to timing of vaccination post treatment with anti-SARS-CoV-2 monoclonal antibodies. Limited safety data are available from the study HV-2093 where COVID-19 vaccine was permitted and no safety concerns were identified. |

**Cardiac effects**

The QT interval prolongation risks of casirivimab and imdevimab have not been assessed but are considered to be low.

**References**

Ronapreve Summary of Product Characteristics, Roche Products Ltd.
REGEN-COV FDA Emergency Use Authorization, Regeneron Pharmaceuticals Inc.
## Chloroquine

### Metabolism
Chloroquine undergoes CYP mediated metabolism by CYPs 2C8, 3A4 and 2D6. Co-administration with inhibitors or inducers of these isoenzymes may increase or decrease exposure to chloroquine respectively and dose changes or additional monitoring could be considered. Mean urinary recovery of chloroquine (within 3-13 weeks) is ~50% of the administered dose, most being unchanged drug and the remainder as metabolite.

### Interaction Potential
- Chloroquine is a moderate inhibitor of CYP2D6 and P-gp and caution may be required when co-administering co-medications metabolized or transported by these pathways with a narrow therapeutic index.
- Concomitant use of multidrug and toxin extrusion protein (MATE1) inhibitors may impact the renal clearance of chloroquine, which could theoretically lead to increased chloroquine concentrations.

### Cardiac effects
Chloroquine has been shown to prolong the QTc interval in some patients and should therefore be used with caution in patients receiving concomitant drugs known to prolong the QT interval or where a drug interaction may increase chloroquine exposure. ECG monitoring would be recommended in these instances.

### References
- Avloclor Tablets *Summary of Product Characteristics*, Alliance Pharmaceuticals.
- Aralen US Prescribing Information, Sanofi Aventis (discontinued).

## Colchicine

### Metabolism
Colchicine is a substrate for both CYP3A4 and the transport protein P-gp.

### Interaction Potential
- Co-administration with P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors will increase the exposure to colchicine, which may lead to colchicine induced toxicity including fatalities.
- If treatment with a P-gp inhibitor or a moderate or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, a reduction in colchicine dosage or interruption of colchicine treatment is recommended
- Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-gp inhibitor or a strong CYP3A4 inhibitor.
- Colchicine does not inhibit or induce CYPs.

### Cardiac effects
A clinical report suggests that colchicine does not have a QT interval prolongation risk

### References
- Colchicine *Summary of Product Characteristics*, Wockhardt UK Ltd.
- Colcrys US Prescribing Information, Takeda Pharmaceuticals America Inc.
**Dexamethasone**

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Dexamethasone is metabolised by CYP3A4.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction</td>
<td></td>
</tr>
<tr>
<td>Potential</td>
<td>Dexamethasone is a moderate inducer of CYP3A4 and P-gp.</td>
</tr>
<tr>
<td></td>
<td>Induction may occur even at low doses.</td>
</tr>
<tr>
<td>Cardiac effects</td>
<td>The QT interval prolongation risk of dexamethasone is considered to be low.</td>
</tr>
</tbody>
</table>

**References**


**Favipiravir**

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Favipiravir is extensively metabolised with only 1% recovered unchanged in urine. The major metabolite is formed by aldehyde oxidase and CYP isoenzymes do not contribute to favipiravir’s metabolism.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction</td>
<td>• Based on metabolism and clearance, clinically significant drug interactions are minimal. Favipiravir is a weak inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 (IC50 &gt;800 μmol/L, 126 μg/mL) and showed little or no induction of CYPs 1A2, 2C9, 2C19 and 3A4 in human hepatocytes.</td>
</tr>
<tr>
<td>Potential</td>
<td>• Favipiravir inhibits CYP2C8 and caution is required in combination with other co-medications metabolised via this route. Favipiravir increased repaglinide Cmax and AUC by 28% and 52% due to inhibition of CYP2C8.</td>
</tr>
<tr>
<td></td>
<td>• Favipiravir is a moderate inhibitor of OAT1 and OAT3.</td>
</tr>
<tr>
<td></td>
<td>• Favipiravir is a mechanism-based inhibitor of aldehyde oxidase <em>in vitro</em>.</td>
</tr>
<tr>
<td></td>
<td>• A study in healthy volunteers increased paracetamol AUC by 14-17% and as a result of this the maximum recommended dose of paracetamol is 3000 mg.</td>
</tr>
<tr>
<td>Cardiac effects</td>
<td>The QT interval prolongation risk of favipiravir is considered to be low.</td>
</tr>
</tbody>
</table>

**References**

- Avigan *Japanese Product Label*, Toyama Chemical Co Ltd.
### Hydrocortisone (oral or IV)

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Hydrocortisone is metabolized by CYP3A4 and is minimally excreted in the urine.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction</td>
<td>• Co-administration with a strong inhibitor of CYP3A4 may increase hydrocortisone exposure.</td>
</tr>
<tr>
<td></td>
<td>• Co-administration with inducers of CYP3A4 may decrease hydrocortisone exposure and decrease its therapeutic effect.</td>
</tr>
<tr>
<td></td>
<td>• Hydrocortisone inhibits the action of anti-diabetics and enhances the actions of coumarin anticoagulants.</td>
</tr>
<tr>
<td></td>
<td>• Hydrocortisone can cause hypokalaemia, and caution must be exercised when coadministering with potassium depletion agents.</td>
</tr>
<tr>
<td>Cardiac effects</td>
<td>No clinically significant effect on QTc prolongation has been observed.</td>
</tr>
<tr>
<td>References</td>
<td>Solu-Cortef Summary of Product Characteristics, Pfizer Ltd.</td>
</tr>
<tr>
<td></td>
<td>Solu-Cortef US Prescribing Information, Pfizer Injectables.</td>
</tr>
</tbody>
</table>

### Hydroxychloroquine

| Note             | Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine. |
| Metabolism       | Hydroxychloroquine undergoes CYP mediated metabolism by CYPs 2C8, 3A4 and 2D6. Co-administration with inhibitors or inducers of these isoenzymes may increase or decrease exposure to hydroxychloroquine respectively and dose changes or additional monitoring could be considered. Hydroxychloroquine and its metabolites are widely distributed in the body and elimination is mainly via the urine, with 3% of the administered dose recovered over 24 hours. |
| Interaction       | • Hydroxychloroquine is a moderate inhibitor of CYP2D6 and P-gp and caution may be required when co-administering co-medications metabolized or transported by these pathways with a narrow therapeutic index. |
|                  | • Concomitant use of multidrug and toxin extrusion protein (MATE1) inhibitors may impact the renal clearance of chloroquine, which could theoretically lead to increased chloroquine concentrations. A similar effect may occur with hydroxychloroquine. |
| Cardiac effects  | Hydroxychloroquine have been shown to prolong the QTc interval in some patients and should therefore be used with caution in patients receiving concomitant drugs known to prolong the QT interval or where a drug interaction may increase chloroquine exposure. ECG monitoring would be recommended in these instances. |
| References       | Plaquenil Summary of Product Characteristics, Zentiva. |
|                  | Plaquenil US Prescribing Information, Concordia. |
### Infliximab

**Metabolism**
The elimination pathways for infliximab have not been characterised but it is likely to be eliminated via its target antigen.

**Interaction Potential**
- Infliximab, per se, has no inhibitory or inducing effects on cytochromes. However, infliximab reverses IL-6 induced suppression of cytochromes (elevation of IL-1 during inflammation has been shown to inhibit CYP3A4, CYP2C19, CYP2C9 and CYP1A2 expression/activity resulting in higher drug exposure of substrate drugs). Upon treatment with infliximab, cytochrome activity normalizes leading to reduced exposure of drugs which, prior to treatment with infliximab, had been adjusted to the metabolism of individuals with various inflammatory conditions.
- Patients infected with COVID19 experience an elevation of IL-6. However, since comediations will not have been adjusted to the acute inflammatory COVID19 state and since treatment with infliximab is initiated rapidly, no a priori adjustment of CYP3A4, CYP2C19, CYP2C9, CYP1A2 substrates is needed. The effect of acute COVID infection on drugs with a narrow therapeutic index is unclear.
- Caution is required when coadministering with myelotoxic drugs due to the potential additive haematological toxicity.
- Coadministration with monoclonal antibodies should be avoided due to the enhanced immunosuppressive effect.
- Use of infliximab with other TNF inhibitors is not recommended.
- Delayed second dosing of COVID vaccines should be avoided in patients treated with infliximab. Anti-SARS-CoV-2 antibody concentrations were shown to be lower in patients treated with infliximab compared to vedolizumab, following a single vaccination dose with the BNT162b2 (Pfizer) and ChAdOx1 nCoV-19 (Oxford-AstraZeneca) SARS-CoV-2 vaccines. Vaccination after SARS-CoV-2 infection, or a second dose of vaccine, led to seroconversion in most patients.

**Cardiac effects**
A formal classification of the QT prolongation risk has not been made.

### References
- Remicade Summary of Product Characteristics, Merck Sharp and Dohme Ltd.
- Remicade US Prescribing Information, Janssen Pharmaceuticals.

### Interferon beta

**Metabolism**
Interferon beta is excreted by hepatic and renal pathways, with renal pathways accountable for about 40% of its clearance.

**Interaction Potential**
- The drug interaction potential of interferons has not been fully evaluated. It has been reported that they may reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. The effect of high-dose interferon beta-1a administration on P450-dependent metabolism in monkeys was evaluated and no changes in liver metabolising capabilities were observed.
- In a small study, interferon-beta was shown to reduce the clearance of theophylline (CYP1A2 substrate) in 6 out of 7 healthy volunteers. The magnitude of the reduction was variable and the clinical relevance of this is unclear, particularly in the acute setting.
- Drugs likely to exacerbate the haematological effects of interferons should be used with caution.

**Cardiac effects**
No clinically significant effect on QTc prolongation has been observed.

**References**
### Ivermectin

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Ivermectin is mainly metabolised by CYP3A4.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Ivermectin is a substrate of P-gp and coadministration with moderate-strong P-gp inhibitors may increase ivermectin transfer across the blood brain barrier, leading to higher concentrations in the brain and increased risk of neurotoxicity.  
  • Coadministration with strong CYP3A4 inhibitors may increase ivermectin exposure.  
  • Coadministration with CYP3A4 inducers may decrease ivermectin exposure, further decreasing the likelihood of reaching efficient concentrations.  
  • Ivermectin may inhibit vitamin-K clotting factors and caution is required when coadministering with vitamin K antagonists. |

<table>
<thead>
<tr>
<th>Cardiac effects</th>
<th>No clinically significant effect on QTc prolongation has been reported.</th>
</tr>
</thead>
</table>
| References | Soolantra Summary of Product Characteristics, Galderma (UK) Ltd.  
Solumectol US Prescribing Information, Merck & Co. Inc. |

### Lopinavir/ritonavir

| Metabolism | Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by CYP3A. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine.  
Ritonavir is a potent CYP3A inhibitor and is given with lopinavir to increase plasma levels of lopinavir. |
|------------|---------------------------------------------------------------------|
| Interaction Potential | • Lopinavir and ritonavir are inhibitors of CYP3A in vitro as well as drug transporters such as P-gp, BCRP and OATP1B1. Lopinavir/ritonavir is likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A or substrates of these drug transporters. Increases in plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events.  
  • Lopinavir/ritonavir has been shown in vivo to induce its own metabolism and to increase the biotransformation of some medicinal products metabolised by cytochrome P450 enzymes (including CYP2C9 and CYP2C19) and by glucuronidation. This may result in lowered plasma concentrations and potential decrease of efficacy of co-administered medicinal products. |

| Cardiac effects | Lopinavir/ritonavir has been shown to cause modest asymptomatic prolongation of the PR interval in some healthy adult subjects. Rare reports of 2nd or 3rd degree atrioventricular block in patients with underlying structural heart disease and pre-existing conduction system abnormalities or in patients receiving drugs known to prolong the PR interval (such as verapamil or atazanavir) have been reported in patients receiving lopinavir/ritonavir. Lopinavir/ritonavir should be used with caution in such patients. |
|----------------|==================================================================|
| References | Kaletra Oral Solution Summary of Product Characteristics, AbbVie Ltd.  
Kaletra US Prescribing Information, AbbVie Inc. |
<table>
<thead>
<tr>
<th><strong>Methylprednisolone (oral or IV)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
</tbody>
</table>
| **Interaction Potential** | • Product labels for methylprednisolone do not recommend coadministration of strong CYP3A4 inhibitors but given the dose of methylprednisolone used in COVID-19 treatment this is unlikely to be clinically significant.  
• Inducers of CYP3A4 may decrease methylprednisolone concentrations and a doubling of methylprednisolone dose would be recommended.  
• Methylprednisolone does not significantly induce or inhibit CYPs. |
| **Cardiac effects** | Cases of QT prolongation with methylprednisolone have been reported but a formal classification of the QT prolongation risk has not been made. |
| **References** | Medrone Summary of Product Characteristics, Pfizer Ltd.  
Medrol US Prescribing Information, Pfizer.  

<table>
<thead>
<tr>
<th><strong>Molnupiravir</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
</tbody>
</table>
| **Interaction Potential** | • Based on in vitro studies, neither molnupiravir nor NHC are inhibitors or inducers of major drug metabolising enzymes or inhibitors of major drug transporters.  
• The potential for molnupiravir or NHC to interact with concomitant medications is considered unlikely. |
| **Cardiac effects** | The effect of molnupiravir on the QT interval has yet to be assessed. |
| **References** | Lagevrio Summary of Product Characteristics, Merck Sharp and Dohme Ltd. |

<table>
<thead>
<tr>
<th><strong>Niclosamide</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
</tbody>
</table>
| **Interaction Potential** | • The likelihood of clinically significant drug interactions is low due to poor bioavailability of the oral formulation of niclosamide and low systemic absorption via the intranasal/inhaled route.  
• Niclosamide does not inhibit or induce CYPs. |
| **Cardiac effects** | No clinically significant effect on QTc prolongation has been reported. |
| **References** | Yomesan Prescribing Information, Bayer (discontinued).  
### Nitazoxanide

**Metabolism**
Following oral administration, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide.

**Interaction Potential**
- In vitro metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes. Although no drug-drug interaction studies have been conducted in vivo, it is expected that no significant interaction would occur when nitazoxanide is co-administered with drugs that either are metabolized by or inhibit cytochrome P450 enzymes.
- Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur (e.g., coumarin derivatives, warfarin, acenocoumarol and phenprocoumon).
- When administered with food the AUC of nitazoxanide in oral form increased by around 50% and subsequently is recommended to be taken with food.

**Cardiac effects**
No clinically significant effect on QTc prolongation have been observed.

**References**
- Alinia US Prescribing Information, Romark Pharmaceuticals.

### Remdesivir

**Metabolism**
Remdesivir is rapidly metabolised following IV administration to GS-704277, GS-441524, and the pharmacologically active metabolite GS-443902.

**Interaction Potential**
- Remdesivir is a prodrug, predominantly metabolized by hydrolase activity.
- Based on rapid distribution, metabolism and clearance the likelihood of clinically significant interactions is low.
- While remdesivir is a substrate of CYP2C8, CYP2D6, CYP3A4 and transporters OATP1B1 and P-gp in vitro, coadministration with inhibitors of these CYP isoforms and transporters is unlikely to increase remdesivir levels.
- Strong inducers are expected to reduce remdesivir to a limited extent (~15-30%) and no a priori dose adjustment of remdesivir is needed when administering with strong inducers.
- Transporter interactions are minimised by the IV route of administration. Rapid clearance means that despite remdesivir being an inhibitor of CYP3A4, OATP1B1/3, BSEP, MRP4 and NTCP in vitro, the potential for clinically significant interactions is low. However, the European Summary of Product Characteristics (but not the US Prescribing Information) for remdesivir suggests that medicinal products that are substrates of CYP3A4 or OATP 1B1/1B3 should be administered at least 2 hours after remdesivir.
- Remdesivir is an inducer of CYP1A2 and potentially CYP3A4 in vitro (increase in mRNA) but considering the exposure it is unlikely to translate into a clinically significant interaction with substrates of these enzymes.
- Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in normal human bronchial epithelial cells.

**Cardiac effects**
Remdesivir does not prolong the QTc interval.

**References**
- Veklury (remdesivir) Summary of Product Characteristics, Gilead Sciences Ltd.
- Veklury (remdesivir) US Prescribing Information, Gilead Sciences Inc.
### Ribavirin

**Metabolism**
Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway; 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Both ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are also excreted renally.

**Interaction Potential**
- *Results of in vitro* studies using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that ribavirin induces liver enzymes. Therefore, there is a minimal potential for P450 enzyme-based interactions.
- Ribavirin inhibits inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine.

**Cardiac effects**
No effect on the QT interval was observed in patients receiving ribavirin in combination with daclatasvir and sofosbuvir.

**References**
- Rebetol *Summary of Product Characteristics*, Merck Sharpe & Dohme Ltd.
- Rebetol *Prescribing Information*, Merck & Co Inc.

### Ruxolitinib

**Metabolism**
Ruxolitinib is mainly metabolised by CYP3A4 (>50%), with some contribution from CYP2C9. Renal excretion accounts for 74% of ruxolitinib clearance and faecal excretion for 22%.

**Interaction Potential**
- *CYP3A4 and/or CYP2C9 inhibitors may increase ruxolitinib exposure*. Use with caution; Ruxolitinib dose should be reduced by half in presence of strong CYP4A4 inhibitors or dual CYP3A4/CYP2C9 inhibitors. No dose adjustment is needed with moderate CYP3A4 inhibitors however monitoring for cytopenia is recommended.
- *CYP3A4 inducers may decrease ruxolitinib exposure*. Monitor and titrate ruxolitinib according to efficacy and safety.
- *Ruxolitinib may inhibit P-gp and BCRP*. Use with caution when coadministering P-gp and/or BCRP substrates with a narrow therapeutic index (i.e. digoxin, DOAC).
- *Drugs likely to exacerbate the haematological effects of ruxolitinib should be used with caution.*
- *There is a risk of additional immunosuppression when ruxolitinib is coadministered with other immunosuppressants*. Coadministration with biological disease-modifying anti-rheumatic drugs or Janus kinase inhibitors is not recommended.

**Cardiac effects**
Ruxolitinib did not prolong QTc at a supratherapeutic dose (200 mg) in healthy subjects.

**References**
- Jakavi *Summary of Product Characteristics*, Novartis Pharmaceuticals Ltd.
**Sarilumab**

**Metabolism**
Sarilumab is an anti-human interleukin 6 (IL-6) receptor monoclonal antibody approved for the treatment of rheumatoid arthritis. Sarilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG and likely undergoes elimination via binding to its target antigen.

**Interaction Potential**
- Sarilumab, *per se*, has no inhibitory or inducing effects on cytochromes. However, sarilumab reverses IL-6 induced suppression of cytochromes (elevation of IL-6 during inflammation has been shown to inhibit CYP3A4, CYP2C19, CYP2C9 and CYP1A2 expression/activity resulting in higher drug exposure of substrate drugs). Upon treatment with sarilumab, cytochrome activity normalizes leading to reduced exposure of drugs which, prior to treatment with sarilumab, had been adjusted to the metabolism of individuals with rheumatoid arthritis.
- Patients infected with COVID19 experience an elevation of IL-6. However, since comedication will not have been adjusted to the acute inflammatory COVID19 state and since treatment with sarilumab is initiated rapidly, no *a priori* adjustment of CYP3A4, CYP2C9, CYP1A2 substrates is needed. The effect of acute COVID infection on drugs with a narrow therapeutic index is unclear.
- Caution is required when coadministering with myelotoxic drugs due to the potential additive haematological toxicity.
- Coadministration with other monoclonal antibodies should be avoided due to the enhanced immunosuppressive effect.

**Cardiac effects**
The QT interval was evaluated in the clinical trials that were part of the rheumatoid arthritis clinical development program. No clinical safety signals related to the QT interval were identified.

**References**
- Kevzara *Summary of Product Characteristics*, Sanofi Genzyme.
- Kevzara *US Prescribing Information*, Sanofi Genzyme.
- Sarilumab *CDER Clinical Review*, Food and Drug Administration.

**Sotrovimab**

**Metabolism**
Sotrovimab is an IgG1 monoclonal antibody and is expected to be degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.

**Interaction Potential**
- Sotrovimab is not metabolized by cytochrome P450 enzymes.
- Interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.
- It is possible that sotrovimab may interfere with the development of effective immune responses to COVID-19 vaccines. Refer to current vaccination guidelines with respect to timing of vaccination post treatment with anti-SARS-CoV-2 monoclonal antibodies. Note, given sotrovimab’s long half life (~49 days) if vaccination is delayed, an interval of greater than that recommended for other antibodies may be required.

**Cardiac effects**
The QT interval prolongation risk for sotrovimab not been assessed but is considered to be low.

**References**
<table>
<thead>
<tr>
<th>Tocilizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
</tbody>
</table>
| **Interaction Potential** | • Tocilizumab, *per se*, has no inhibitory of inducing effects on cytochromes. However, tocilizumab reverses IL-6 induced suppression of cytochromes (elevation of IL-6 during inflammation has been shown to inhibit CYP3A4, CYP2C19, CYP2C9 and CYP1A2 expression/activity resulting in higher drug exposure of substrate drugs). Upon treatment with tocilizumab, cytochrome activity normalizes leading to reduced exposure of drugs which, prior to treatment with tocilizumab, had been adjusted to the metabolism of individuals with rheumatoid arthritis.  
• Patients infected with COVID19 experience an elevation of IL-6. However, since comedications will not have been adjusted to the acute inflammatory COVID19 state and since treatment with tocilizumab is initiated rapidly, *no a priori* adjustment of CYP3A4, CYP2C9, CYP1A2 substrates is needed. The effect of acute COVID infection on drugs with a narrow therapeutic index is unclear.  
• Caution is required when coadministering with myelotoxic drugs due to the potential additive haematological toxicity.  
• Coadministration with other monoclonal antibodies should be avoided due to the enhanced immunosuppressive effect |
| **Cardiac effects** | No clinically significant effect on QT prolongation was observed in healthy subjects at therapeutic (10 mg/kg) and supratherapeutic (20 mg/kg) doses. |
| **References** | RoActemra (for infusion) *Summary of Product Characteristics*, Roche Products Ltd.  
RoActemra (for injection) *Summary of Product Characteristics*, Roche Products Ltd.  
Actemra *US Prescribing Information*, Genentech Inc. |