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 Therefore, the quality of evidence for all unpublished data should be regarded as very low.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.
### Anakinra

**Metabolism**
Anakinra is recombinant human interleukin-1 (IL-1) receptor antagonist and is eliminated by glomerular filtration and subsequent tubular metabolism.

**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 comedications 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

**Metabolism**
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%.

**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

Metabolism
Azithromycin is extensively metabolised and is mainly eliminated via biliary excretion with animal data suggesting that this may occur via P-gp and MRP2.

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.

Baricitinib

Metabolism
Baricitinib metabolism is mediated by CYP3A4, with <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.

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 USA.
**Chloroquine and Hydroxychloroquine**

<table>
<thead>
<tr>
<th>Note</th>
<th>Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine.</th>
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<tbody>
<tr>
<td>Metabolism</td>
<td>Chloroquine and hydroxychloroquine undergo 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. 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.</td>
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</table>
| Interaction Potential | - Chloroquine and hydroxychloroquine are moderate inhibitors 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 | Chloroquine and 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 | Chloroquine  
Avloclor Tablets Summary of Product Characteristics, Alliance Pharmaceuticals.  
Malarivon Summary of Product Characteristics, Wallace Manufacturing Chemists.  
Aralen US Prescribing Information, Sanofi Aventis (discontinued).  
Hydroxychloroquine  
Plaque US Prescribing Information, Concordia. |

**Dexamethasone**

| Metabolism | Dexamethasone is metabolised by CYP3A4. |
| Interaction Potential | - Dexamethasone is a moderate inducer of CYP3A4 and P-gp.  
- Induction may occur even at low doses. |
| Cardiac effects | The QT interval prolongation risk of dexamethasone is considered to be low. |
### 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>
</table>
| Interaction Potential | • 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 >800 μmol/L, 126 μg/mL) and showed little or no induction of CYPs 1A2, 2C9, 2C19 and 3A4 in human hepatocytes.  
• 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.  
• Favipiravir is a moderate inhibitor of OAT1 and OAT3.  
• Favipiravir is a mechanism-based inhibitor of aldehyde oxidase in vitro.  
• 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. |
| Cardiac effects | The QT interval prolongation risk of favipiravir is considered to be low. |
| References | Avigan *Japanese Product Label*, Toyama Chemical Co Ltd.  

### Interferon beta

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Interferon beta is excreted by hepatic and renal pathways, with renal pathways accountable for about 40% of its clearance.</th>
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</table>
| 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. |
### Ivermectin

<table>
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<tr>
<th>Metabolism</th>
<th>Ivermectin is mainly metabolised by CYP3A4.</th>
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</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. |
| Cardiac effects | No clinically significant effect on QTc prolongation has been reported. |
| References | Soolantra Summary of Product Characteristics, Galderma (UK) Ltd.  
  Stromectol US Prescribing Information, Merck & Co. Inc. |

### Lopinavir/ritonavir

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>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.</th>
</tr>
</thead>
</table>
| 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. |
### Nitazoxanide

<table>
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<tr>
<th>Metabolism</th>
<th>Following oral administration, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide</th>
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</table>
| 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

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Remdesivir is rapidly metabolised following IV administration to GS-704277, GS-441524, and the pharmacologically active metabolite GS-443902.</th>
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</thead>
</table>
| 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  
• Remdesivir can be impacted by strong inducers thus coadministration is not recommended.  
• 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 FDA Emergency Use Authorization) 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 CYP2B6 *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.
Remdesivir *FDA Emergency Use Authorization*, 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 of 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 comedications 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.

Tocilizumab

**Metabolism**
Tocilizumab is an anti-human interleukin 6 (IL-6) receptor monoclonal antibody approved for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. Tocilizumab likely undergoes elimination via binding to its target antigen.

**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.