Evaluating the drug-drug interaction risk of COVID-19 therapies (licensed or under clinical investigation)

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-medication 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 Therefore, the quality of evidence for all unpublished data should be regarded as very low.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 COVID-19 therapies (licensed and under clinical investigation) 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 risk 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 COVID therapies which are either licensed or under clinical investigation:

- Anakinra
- Bamllanivimab / Etesevimab
- Bebtelovimab
- Baricitinib
- Budesonide (inhaled)
- Canakinumab
- Casirivimab / Imdevimab
- Dexamethasone
- Favipiravir
- Flavoxamine
- Hydrocortisone (oral or IV)
- Imatinib
- Infliximab
- Methylprednisolone (oral or IV)
- Molnupiravir
- Niclosamide
- Nirmatrelvir + ritonavir
- Nitazoxanide
- Remdesivir
- Ruxolitinib
- Sarilumab
- Sotrovimab
- Tixagevimab/ Cilgavimab
- Tocilizumab

(Click the drug name to view the metabolic details)
**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 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. |

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**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. |
## Bebtelovimab

### Metabolism
Bebtelovimab is an IgG1 monoclonal antibody and is expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

### Interaction Potential
- Bebtelovimab 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 bebtelovimab 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 risk for bebtelovimab has not been assessed but is considered to be low.

### References
- Bebtelovimab FDA Emergency Use Authorization, Lilly USA.

## 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.
### Budesonide (inhaled)

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Budesonide is a CYP3A4 substrate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction</td>
<td>• Budesonide does not inhibit or induce CYPs.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
</tbody>
</table>

#### 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.


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### 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>
<tbody>
<tr>
<td>Interaction</td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• 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 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.</td>
</tr>
<tr>
<td></td>
<td>• Caution is required when coadministering with myelotoxic drugs due to the potential additive haematological toxicity.</td>
</tr>
<tr>
<td></td>
<td>• Caution is required when coadministering with monoclonal antibodies should be avoided due to the potential immunosuppressive effect.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
</tbody>
</table>

#### 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.
Evaluating the drug-drug interaction risk of COVID-19 therapies (licensed or under clinical investigation)

# Casirivimab / Imdevimab

**Metabolism**
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.

**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.

# Dexamethasone

**Metabolism**
Dexamethasone is metabolised by CYP3A4.

**Interaction Potential**
- Dexamethasone is a dose-dependent inducer of CYP3A4 and is regarded as a moderate inducer of CYP3A4.
- However, at the low doses used for the treatment of COVID-19, dexamethasone shows weak induction of CYP3A4 and P-gp.

**Cardiac effects**
The QT interval prolongation risk of dexamethasone is considered to be low.

**References**


Oral and inhaled corticosteroids: differences in P-glycoprotein (ABCB1) mediated efflux.

The effect of dexamethasone on the pharmacokinetics of triazolam.
### Favipiravir

**Metabolism**
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.

**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.

### Fluvoxamine

**Metabolism**
Fluvoxamine is extensively metabolized, mainly by CYP2D6 and to a lesser extent by CYP1A2. Caution is indicated in patients known to have reduced levels of CYP2D6 activity (CYP2D6 “poor metabolizers”). Fluvoxamine mean Cmax, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in 13 poor metabolizers when compared to data from 16 extensive metabolizers.

**Interaction Potential**
- Fluvoxamine is a strong inhibitor of CYP1A2 and CYP2C19.
- Fluvoxamine is a moderate inhibitor of CYP3A4, CYP2C9 and CYP2D6.
- Coadministration of fluvoxamine with other serotonergic drugs may increase the risk of serotonin syndrome.

**Cardiac effects**
Fluvoxamine has a conditional risk of QT prolongation and/or TdP on the CredibleMeds.org website. Increased plasma concentrations may result in a higher risk for QT-prolongation/Torsade de Pointes.

**References**
- Faverin Summary of Product Characteristics, Mylan.
- Luvox US Prescribing Information, ANI Pharmaceuticals Inc.
## 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>• Coadministration with a strong inhibitor of CYP3A4 may increase hydrocortisone exposure.</td>
</tr>
<tr>
<td>Potential</td>
<td>• Coadministration with inducers of CYP3A4 may decrease hydrocortisone exposure and decrease its</td>
</tr>
<tr>
<td></td>
<td>therapeutic effect.</td>
</tr>
<tr>
<td></td>
<td>• Hydrocortisone inhibits the action of anti-diabetics and enhances the actions of coumarin</td>
</tr>
<tr>
<td></td>
<td>anticoagulants.</td>
</tr>
<tr>
<td></td>
<td>• Hydrocortisone can cause hypokalaemia, and caution must be exercised when coadministering with</td>
</tr>
<tr>
<td></td>
<td>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>

## Imatinib

| Metabolism           | Imatinib is metabolized mainly by CYP3A4. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, |
|                      | CYP2C9, and CYP2C19, play a minor role in its metabolism.                                       |
| Interaction          | • Imatinib is a moderate inhibitor of CYP3A4 and CYP2C9.                                       |
| Potential            | • Imatinib is a weak inhibitor of CYP2D6.                                                        |
| Cardiac effects      | Imatinib has a possible risk of QT prolongation and/or TdP on the CredibleMeds.org website.      |
|                      | However, the risk of QT interval prolongation when imatinib is used as a COVID-19 therapy is     |
|                      | considered to be low in the absence of a significant pharmacokinetic interaction given the dose   |
|                      | and duration of treatment.                                                                       |
| References           | Glivec Summary of Product Characteristics, Novartis Pharmaceuticals.                            |
|                      | Gleevec US Prescribing Information, Novartis Pharmaceuticals.                                   |
### Infliximab

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>The elimination pathways for infliximab have not been characterised but it is likely to be eliminated via its target antigen.</th>
</tr>
</thead>
</table>
| 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-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 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 comedication 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.  
• Co-administration 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.  

### Methylprednisolone (oral or IV)

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Methylprednisolone is mainly metabolized by CYP3A4 and may be a substrate for P-gp.</th>
</tr>
</thead>
</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.  
### Molnupiravir

**Metabolism**
Molnupiravir is hydrolysed to n-hydroxycytidine (NHC) prior to reaching systemic circulation. Uptake of NHC and metabolism to NHC-TP are mediated by the same pathways involved in endogenous pyrimidine metabolism. NHC is not a substrate of major drug metabolising enzymes or transporters.

**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.
- Molnupiravir FDA Emergency Use Authorization, Merck & Co Inc.

### Niclosamide

**Metabolism**
Niclosamide is metabolized by CYP1A2 and UGT1A1.

**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).
### Evaluating the drug-drug interaction risk of COVID-19 therapies (licensed or under clinical investigation)

**Nirmatrelvir + ritonavir**

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Nirmatrelvir (PF-07321332) is a substrate for CYP3A and P-gp. The primary route of elimination of nirmatrelvir when administered with ritonavir is renal excretion of intact drug. Approximately 49.6% and 35.3% of the administered dose of nirmatrelvir 300 mg was recovered in urine and faeces, respectively. Ritonavir is a potent CYP3A inhibitor and is given with nirmatrelvir to increase plasma levels and half-life of nirmatrelvir. Ritonavir causes a mechanism-based inhibition which resolves for a large part approximately 3 days after ritonavir is discontinued in most young and elderly individuals.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Nirmatrelvir/ritonavir may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Since the onset of inhibition is rapid, clinically significant drug-drug interactions may occur even if nirmatrelvir/ritonavir is given for a short treatment course.  
• Due to the short duration (5 days) of treatment for COVID-19, management of some drug-drug interactions with nirmatrelvir/ritonavir may differ from those when ritonavir is prescribed for long-term use as a booster for HIV protease inhibitors. Please use the COVID website for details of drug-drug interactions with nirmatrelvir/ritonavir.  
• Potent CYP3A inducers may significantly reduce nirmatrelvir or ritonavir plasma concentrations which may be associated with the potential for loss of virologic response and possible resistance.  
• Nirmatrelvir does not reversibly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 in vitro at clinically relevant concentrations.  
• Nirmatrelvir does not induce any CYPs at clinically relevant concentrations.  
• Based on in vitro data, nirmatrelvir has a low potential to inhibit BCRP, MATE2K, OAT1, OAT3, OATP1B3 and OCT2. There is a potential for nirmatrelvir to inhibit MDR1, MATE1, OCT1 and OATP1B1 at clinically relevant concentrations.  
• Ritonavir is an inhibitor of CYP3A4, CYP2D6 and P-gp.  
• Ritonavir may induce CYP1A2, CYP2C8, CYP2C9, CYP2C19 and glucuronidation. This is unlikely to be clinically significant as induction reaches maximal effect after several days and nirmatrelvir/ritonavir treatment is of a short duration (5 days). |
| Cardiac effects | No clinically relevant effect of nirmatrelvir on QTcF interval was observed in a double-blind, randomised, placebo-controlled, cross-over study in 10 healthy adults. |
| References | Paxlovid Summary of Product Characteristics, Pfizer Ltd.  
Paxlovid FDA Emergency Use Authorization, Pfizer Inc.  
# Evaluating the drug-drug interaction risk of COVID-19 therapies (licensed or under clinical investigation)

## Nitazoxanide

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>Following oral administration, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction Potential</td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>• Tizoxanide is highly bound to plasma protein (&gt;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).</td>
<td></td>
</tr>
<tr>
<td>• When administered with food the AUC of nitazoxanide in oral form increased by around 50% and subsequently is recommended to be taken with food.</td>
<td></td>
</tr>
</tbody>
</table>

## Cardiac effects

No clinically significant effect on QTc prolongation have been observed.

## References


# 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>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction Potential</td>
<td></td>
</tr>
<tr>
<td>• Remdesivir is a prodrug, predominantly metabolized by hydrolase activity.</td>
<td></td>
</tr>
<tr>
<td>• Based on rapid distribution, metabolism and clearance the likelihood of clinically significant interactions is low.</td>
<td></td>
</tr>
<tr>
<td>• While remdesivir is a substrate of CYP2C8, CYP2D6, CYP3A4 and transporters OATP1B1 and P-gp <em>in vitro</em>, coadministration with inhibitors of these CYP isosforms and transporters is unlikely to increase remdesivir levels</td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>• 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 <em>in vitro</em>, 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.</td>
<td></td>
</tr>
<tr>
<td>• Remdesivir is an inducer of CYP1A2 and potentially CYP3A4 <em>in vitro</em> (increase in mRNA) but considering the exposure it is unlikely to translate into a clinically significant interaction with substrates of these enzymes.</td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
</tbody>
</table>

## 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.)
### 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.
- Jakafi US Prescribing Information, Incyte Corporation.

### 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.
# 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.

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

## References
- Xevudy (sotrovimab) Summary of Product Characteristics, GlaxoSmithKline.
- Sotrovimab FDA Emergency Use Authorization, GlaxoSmithKline.

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# Tixagevimab/ Cilgavimab

## Metabolism
Tixagevimab and cilgavimab 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. Based on pharmacokinetic modelling, COVID-19 vaccination following tixagevimab/cilgavimab administration had no clinically relevant impact on the clearance of tixagevimab and cilgavimab.

## Interaction Potential
- Tixagevimab and cilgavimab 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 tixagevimab and cilgavimab 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.
- The American Centers for Disease Control and Prevention advise that tixagevimab/cilgavimab used for pre-exposure prophylaxis (PrEP) should be administered at least two weeks after vaccination. Check local guidelines.

## Cardiac effects
The QT interval prolongation risks for tixagevimab and cilgavimab have not been assessed but are considered to be low.

## References
- Evusheld Summary of Product Characteristics, AstraZeneca.
Evaluating the drug-drug interaction risk of COVID-19 therapies (licensed or under clinical investigation)

### Tocilizumab

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>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.</th>
</tr>
</thead>
</table>
| Interaction Potential | • Tocilizumab, *per se*, has no inhibitory or 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 comedication 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. |