How we make our evaluations

The scale in use of experimental therapies for COVID19 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 Therefore, the quality of evidence for all unpublished data should be regarded as very low.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 experimental therapies, and the basis on which our DDI evaluations have been made. Please note that for drugs already listed on our HIV and HEP websites, interactions when used for COVID may be different due to the short duration of treatment.

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 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.

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).

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.

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

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. • 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.

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.

Chloroquine and Hydroxychloroquine	
Note	*Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine.*
Metabolism	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.
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.
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.

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 carboxyacid 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.

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.