MACROLIDES DRUG INTERACTIONS TABLE V2.1

This information on drug interactions with antimicrobials is intended for use as a guide and not as a complete reference source. Further information is available in the SmPCs of the individual medicines (section 4.5) available at www.HPRA.ie, the BNF Appendix 1 and Stockley's Drug Interactions. Please be aware that new evidence may emerge that may overtake some of these recommendations.

It is important to note that macrolides have many drug interactions due to enzyme inhibition (CYP3A4) and effects on QT interval prolongation. The list provided is not exhaustive. Check for interactions against patient's medication before prescribing. Consult product SmPC (section 4.5) for full list of interacting medicines

Antibiotic Class	Interacting Drug	Comment
Macrolides, e.g. • **Azithromycin** • **Clarithromycin** • **Erythromycin** *(continued on the next 3 pages)*	**Statins**	Risk of myopathy with rare reports of rhabdomyolysis. Warn patients to report signs of myopathy (e.g. muscle pain or weakness). Simvastatin: erythromycin & clarithromycin are contraindicated. If treatment with erythromycin & clarithromycin cannot be avoided, suspend simvastatin for duration of antibiotic course and for 7 days after last antibiotic dose. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. Atorvastatin: Temporarily withhold the statin or, if necessary, give the lowest possible statin dose. + Clarithromycin: If on doses >20mg atorvastatin, reduce to 20mg for duration of macrolide treatment. Pravastatin: + Clarithromycin: Limit the pravastatin dose to 40 mg daily.
	Warfarin	Risk of bleeding. INR should be checked within the first 3 days of starting, during therapy and after discontinuation with warfarin dosage adjusted accordingly.

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	Interacting Drug	Comment
Macrolides, e.g. • **Azithromycin** • **Clarithromycin** • **Erythromycin** *(continued from previous page and on the next 2 pages)*	**DOACs -** **Dabigatran, Rivaroxaban, Apixaban, Edoxaban**	Dabigatran: increased levels of dabigatran, monitor for adverse effects (such as bleeding). Discontinue dabigatran if bleeding occurs. Rivaroxaban: may increase levels, usually not clinically significant. Monitor for signs of bleeding. Apixaban: monitor for signs and symptoms of bleeding. Edoxaban: risk of increased exposure: refer to individual product literature.
	Drugs that prolong QT interval * **Non-drug risk factors for prolonged QT interval: Family history, Increasing age, female sex, electrolyte abnormalities (hypokalaemia, hypocalcaemia, hypomagnesaemia), cardiac ischaemia, cardiomyopathies, hypothyroidism and hypoglycaemia.*	Macrolides are strongly advised against in patients on medications that prolong the QT interval: Consider alternatives or seek advice e.g. antipsychotic medication including atypical antipsychotics (clarithromycin and erythromycin are contraindicated with quetiapine), amiodarone & other anti-arrhythmics, some antidepressants (tricyclic antidepressants, SSRIs and MAOIs), alfuzosin, domperidone, galantamine, indapamide, lithium, methadone, quinine sulphate, tamoxifen, tizanidine, hydroxyzine, ranolazine, ivabradine. **This is not a complete list, for a more extensive list of drugs that can prolong QT Interval please consult the relevant SmPC on** HPRA website**, the BNF or** www.crediblemeds.org **for further information.** **NB: Consider OTC medication e.g. domperidone is contraindicated with the macrolides.**
	Colchicine	Clarithromycin, erythromycin and azithromycin are predicted to increase risk of colchicine exposure. Concomitant administration of clarithromycin and colchicine is contraindicated.

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	Interacting Drug	Comment
Macrolides, e.g. • **Azithromycin** • **Clarithromycin** • **Erythromycin** *(continued on the previous 2 pages and on the next page)*	**Antiepileptic drugs**	Increased plasma concentrations of carbamazepine with clarithromycin and erythromycin, phenytoin with clarithromycin and possibly valproate with erythromycin. Patients should report any symptoms of toxicity (dizziness, diplopia, ataxia, mental confusion). Dose adjustments may be necessary. Consult individual SPCs.
	Oral hypoglycemic agents/Insulin	Concomitant use can result in hypoglycaemia. Careful monitoring of glucose is recommended.
	Benzodiazepines & Z-Drugs	Concomitant administration of oral midazolam and clarithromycin is contraindicated. Increase in exposure to alprazolam, triazolam and midazolam expected with clarithromycin and erythromycin. Monitor for increase in adverse effects (e.g. sedation). Similar effects expected with some Z-drugs (e.g. zopiclone). Caution with driving/skilled tasks. Consult individual product SPCs.
	Digoxin	Increase in exposure to digoxin. Monitor for signs of digoxin toxicity (e.g. bradycardia).
	Immunosuppressant medications: **Ciclosporin, Tacrolimus, Sirolimus**	Increased plasma levels of anti-rejection medicines expected. See individual SPCs for recommendations.
	Ticagrelor	Contraindicated with clarithromycin due to marked increase in Ticagrelor exposure, caution use with azithromycin.
	Tolterodine	Avoid concurrent use with clarithromycin.
	Eplerenone	+ *Clarithromycin:* Contraindicated *Erythromycin:* Maximum eplerenone dose of 25 mg daily.
	Salmeterol (inhaled systemic)	Avoid with clarithromycin.

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	Interacting Drug	Comment
Macrolides, e.g. • **Azithromycin** • **Clarithromycin** • **Erythromyci** *(continued from the previous 3 pages*	**HR-Calcium channel blockers (Diltiazem, Verapamil)**	*Clarithromycin/ Erythromycin:* Monitor for adverse effects (e.g. bradycardia, hypotension, headache, oedema) and reduce the calcium-channel blocker dose as necessary.
	Lercanidipine	Contraindicated with clarithromycin and erythromycin - markedly increased exposure to lercanidipine.
	Phosphodiesterase inhibitors: Sildenafil, Tadalafil, Vardenafil	Macrolides can increase exposure to PDE5 inhibitors. Dose adjustment may be required. Consult individual SPCs.
	Aminophylline, Theophylline	Theophylline clearance (from aminophylline) can be reduced by erythromycin. In some cases this has led to raised theophylline levels, and toxicity may develop. Consider giving a non-interacting antibacterial if possible. With clarithromycin and azithromycin, consider an interaction if any unexplained reduction in theophylline efficacy or theophylline adverse effects (headache, nausea, tremor) occur.
	Eletriptan	Concurrent use with clarithromycin and erythromycin should be avoided.

Combined Hormonal Contraception
Extra precautions are no longer required when using combined hormonal contraception (CHC) with antibiotics (unless those antibiotics are enzyme inducers e.g. rifampicin, rifabutin). The usual additional precautions regarding vomiting, diarrhoea and non-adherence to CHC apply. Correct contraceptive practice must be adhered to.

The National Medicines Information Centre (NMIC) clinical enquiry answering service is available to prescribers in Ireland for further information about a specific drug-drug interaction(s). Contact details for the NMIC are available here.