

## Supplement 1. Lipid-lowering medications in Singapore

Table 2. Overview of lipid-lowering medications registered in Singapore

Medication*	Dosing recommendations	Dose adjustment in renal impairment <sup>†</sup>	Common side effects	Additional considerations (contraindications, precautions, monitoring)
<b>Statin: inhibits the HMG-CoA reductase enzyme, increasing the uptake of cholesterol and inhibiting hepatic synthesis</b>				
Atorvastatin	10–80 mg daily	Not required	Headache, myalgia, fatigue, constipation, dizziness, nausea, abdominal pain, hyperglycaemia	Usual dose range applies in patients with mild hepatic impairment (Child-Pugh score class A) Elevated CK at baseline >5x ULN: investigate cause before considering statin initiation <b>Rosuvastatin:</b> Regular monitoring of renal function and specialist supervision is recommended if treated with 40 mg dose. <b>Contraindication:</b> Decompensated cirrhosis or acute liver failure. The manufacturer advises against use of statin in active liver disease or unexplained persistent transaminase elevations.
Lovastatin	20–80 mg daily, with evening meal	CrCl <30: caution with >20 mg daily		
Pitavastatin	1–4 mg daily	CrCl 15–60: initial 1 mg daily, up to 2 mg daily		
Pravastatin	10–40 mg daily	Moderate to severe renal impairment: initial dose 10 mg daily		
Rosuvastatin	Initial: 5 mg daily for Asian patients Maintenance: up to 20 mg daily Higher doses than 20 mg should be prescribed with caution in Asian patients	Not required for mild renal impairment CrCl <60: doses above 20 mg should not be used CrCl <30: contraindicated		
Simvastatin	5–40 mg daily 80 mg: use should be limited to patients who have been taking 80mg long-term without myopathy.	Not required		
<b>Cholesterol absorption inhibitor: inhibits the absorption of cholesterol, leading to reduced hepatic stores and increasing clearance of cholesterol</b>				
Ezetimibe	10 mg daily	Not required If eGFR <60 mL/min/1.73 m <sup>2</sup> and used with simvastatin: Caution with simvastatin doses >20 mg daily	Arthralgia, dizziness, upper respiratory tract infection, diarrhoea, GGT increased (With statin) AST or ALT increased, myalgia, fatigue, headache	Hepatic impairment: No dosage adjustment is necessary for patients with mild impairment. Not recommended in moderate or severe (Child-Pugh class B and C) hepatic impairment <b>Co-administration with other lipid-lowering medications:</b> • Statins: Liver function test should be performed if added on to a statin. • Fibrates: Fenofibrate is the only fibrate that has been co-administered with ezetimibe <b>Contraindication:</b> Active liver disease or unexplained persistent transaminase elevations
<b>Fibrate: activation of peroxisome proliferator activated receptor type alpha (PPARα) and increases the lipolysis of triglyceride-rich particles</b>				
Fenofibrate	Multiple formulations exist - refer to institutional formulary when using information below. Fenofibrate 145 mg tablet (nanoparticles): 1 tab daily Fenofibrate (micronised) 160 mg tablet: 1 tab daily with food Fenofibrate capsule (100 mg, 160 mg, 200 mg, 300 mg): refer to product-specific prescribing information as dosing varies	CrCl 30–59: if available, start with 100 mg standard capsule. CrCl <30: contraindicated	Abdominal pain, nausea, vomiting, diarrhoea, flatulence, transaminases increased	Monitor the risk of myopathy if used with a statin and consult product information for dosing advice. Review the indication and consider reducing or stopping fenofibrate if appropriate. <b>Contraindication:</b> Not recommended for patients with hepatic impairment <b>Monitoring:</b> Transaminases should be monitored periodically. Renal monitoring should be considered for patients at risk of renal impairment.

Medication*	Dosing recommendations	Dose adjustment in renal impairment <sup>^</sup>	Common side effects	Additional considerations (contraindications, precautions, monitoring)
Choline fenofibrate	MR capsules: 135mg daily for mixed hyperlipidaemia; 45–135 mg daily for severe hypertriglyceridaemia	CrCl 30–80: initial 45 mg daily CrCl <30: contraindicated	Abdominal pain, nausea, vomiting, diarrhea, flatulence, transaminases increased	Hepatic impairment: Not studied in patients with hepatic impairment
Bezafibrate	200 mg TDS	CrCl <15: avoid	Decreased appetite, GI disorder	<b>Monitoring:</b> liver function and creatine kinase when used in conjunction with statin
Pemafibrate	0.1–0.2 mg BD	eGFR <30: Use a low starting dose; max 0.2 mg daily	Cholelithiasis	<b>Contraindication:</b> Child-Pugh grade B or C, biliary obstruction, cholelithiasis <b>Monitoring:</b> liver function
Gemfibrozil	1200 mg daily in 2 divided doses, 30 min before morning and evening meal	eGFR 30–80: initial 900 mg daily eGFR <30: contraindicated	Constipation, diarrhoea, fatigue, flatulence, GI discomfort, headache, nausea, skin reactions, vertigo, vomiting	<b>Contraindication:</b> gallbladder or biliary tract disease, use with simvastatin <b>Monitoring:</b> blood count for first year of use; liver function; creatine kinase when used in conjunction with statin
<b>PCSK9 inhibitor</b>				
<b>Monoclonal antibody: inhibits the binding of PCSK9 to LDL-C receptors, increasing LDL-C receptors and enhancing clearance of cholesterol from the blood.</b>				
Evolocumab (only 140 mg/mL injection registered in Singapore at present)	SC 140 mg once every 2 weeks or 420 mg once monthly	Not required eGFR <30: Limited experience and data; use with caution	Injection site reactions, upper respiratory tract signs and symptoms, pruritus, arthralgia, back pain	Hepatic impairment: Limited experience in severe hepatic impairment (Child-Pugh class C). No dose adjustment is needed for patients with mild or moderate hepatic impairment. Patient or caregiver should be counselled on subcutaneous injection technique and how to handle missed doses.
Alirocumab (only 75 mg/mL and 150 mg/mL injections registered in Singapore at present)	SC 75 mg once every 2 weeks or 300 mg once monthly SC 150 mg once every 2 weeks may be considered for those requiring >60% LDL-C reduction	No dose adjustment is needed for patients with mild or moderate renal impairment eGFR <30: Limited experience and data; use with caution		
<b>PCSK9 inhibitor</b>				
<b>Double-stranded small interfering ribonucleic acid (siRNA): directs breakdown of mRNA for PCSK9, increasing LDL-C receptors and enhancing clearance of cholesterol from the blood.</b>				
Inclisiran	SC 284 mg initially, again at 3 months, then every 6 months	Not required eGFR <30: Limited experience	Injection site reactions (pain, rash, erythema)	Hepatic impairment: Limited experience in severe hepatic impairment (Child-Pugh class C). No dose adjustment is needed for patients with mild or moderate hepatic impairment. Inclisiran is to be administered by a healthcare professional.
<b>Bile acid sequestrants: bind bile acids and promote hepatic conversion of cholesterol into bile acids, increasing LDL-C receptors and clearing LDL-C from the blood</b>				
Cholestyramine	Initially 4 g daily, increase to 12–16 g in 1 to 4 divided doses before meals. Max dose may vary depending on product – refer to leaflet.	Not required	Constipation, GI discomfort, headache, nausea, vomiting	<b>Contraindication:</b> Complete biliary obstruction Hyperchloraemic acidosis have been reported.

\* Includes medications with single active ingredient registered in Singapore. For fixed-dose combination products, refer to information on individual components. Information is referenced from local product inserts or consolidated product monographs; refer to product inserts for full details before prescribing. Information from other references (e.g. international guidelines) may differ. Clinical judgement should be exercised at all times when making decisions for an individual patient.

<sup>^</sup> Renal dose adjustment in dialysis is excluded from this table.

Abbreviations - ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance (in mL/min); eGFR, estimated glomerular filtration rate (in mL/min/1.73m<sup>2</sup>); GGT, gamma-glutamyl transferase; ULN, upper limit of normal

Table 3. Selected interactions with commonly used medications that may increase the risk of statin side effects

Statin	Medication	Recommendation**
All statins	Colchicine	Monitor signs and symptoms of myopathy
	Gemfibrozil	Avoid; if gemfibrozil must be used, rosuvastatin 10mg daily may be considered
	Fenofibrate	Monitor signs and symptoms of myopathy Max dose of rosuvastatin: 10 mg daily
Atorvastatin	Clarithromycin (oral)	Max dose of atorvastatin 20 mg daily
	Erythromycin (oral)	Monitor signs and symptoms of myopathy
	Fluconazole (oral)	Monitor signs and symptoms of myopathy
	Itraconazole (oral)	Max dose of atorvastatin 20 mg daily
	Sacubitril and valsartan combination	Consider lower doses and monitor signs and symptoms of myopathy, or use other statins
	Verapamil	Consider lower doses of atorvastatin and monitor signs and symptoms of myopathy
Lovastatin	Amlodipine	Monitor signs and symptoms of myopathy; consider limiting lovastatin dose to 20 mg daily
	Amiodarone	Max dose of lovastatin 40 mg daily
	Clarithromycin (oral)	Avoid; stop statin temporarily to complete course of treatment if clarithromycin is needed
	Diltiazem	Max dose of lovastatin 20 mg daily
	Erythromycin (oral)	Avoid
	Fluconazole (oral)	Monitor signs and symptoms of myopathy
	Itraconazole (oral)	Avoid; lovastatin is contraindicated during and for 2 weeks after treatment with itraconazole
	Ticagrelor	Max dose of lovastatin 40 mg daily
	Verapamil	Max dose of lovastatin 20 mg daily
Pitavastatin	Erythromycin (oral)	Max dose of pitavastatin 1 mg daily
Pravastatin	Clarithromycin (oral)	Max dose of pravastatin 40 mg daily
Rosuvastatin	Clopidogrel	Max dose of rosuvastatin 20 mg daily
Simvastatin	Amlodipine	Max dose of simvastatin 20 mg daily
	Amiodarone	Max dose of simvastatin 20 mg daily
	Clarithromycin (oral)	Avoid; stop statin temporarily to complete course of treatment if clarithromycin is needed
	Diltiazem	Avoid using simvastatin doses greater than 10 mg/day and diltiazem doses greater than 240 mg/day
	Erythromycin (oral)	Avoid
	Fluconazole (oral)	Monitor signs and symptoms of myopathy
	Itraconazole (oral)	Avoid; simvastatin is contraindicated during and for 2 weeks after treatment with itraconazole
	Nirmatrelvir and ritonavir combination (Paxlovid)	Stop statin temporarily to complete course of treatment
	Ticagrelor	Max dose of simvastatin 40 mg daily
Verapamil	Max dose of simvastatin 10 mg daily	

\*\* Refer to drug interactions checker for full details on management and other medications.