

**Evidence-based recommendations to improve the safe use of drugs in patients with liver cirrhosis***Drug safety*

**Authors:** Rianne A. Weersink, Margriet Bouma, David M. Burger, Joost P.H. Drenth, S. Froukje Harkes-Idzinga, Nicole G.M. Hunfeld, Herold J. Metselaar, Margje H. Monster-Simons, Katja Taxis, Sander D. Borgsteede

**Correspondence to:** Rianne A. Weersink. Affiliations: the Health Base Foundation and the University of Groningen. Email: rianne.weersink@healthbase.nl

**Supplementary Table 1. Overview of recommendations in which the safety class is depending on the severity of liver cirrhosis (Child-Pugh classification [16]).**

Drug	Severity of liver cirrhosis		
	Child-Pugh A	Child-Pugh B	Child-Pugh C
Alfentail	No additional risks known	No additional risks known	Unknown
Alogliptin	No additional risks known	No additional risks known	Unknown
Benazepril	No additional risks known	Additional risks known	Unsafe
Bezafibrate	No additional risks known	Unknown	Unknown
Canagliflozin	No additional risks known	No additional risks known	Unknown
Candesartan	No additional risks known	Additional risks known	Unsafe
Captopril	No additional risks known	Additional risks known	Unsafe
Clopidogrel	No additional risks known	No additional risks known	Unsafe
Codeine	Additional risks known	Unsafe	Unsafe
Dasabuvir	No additional risks known	Additional risks known	Unsafe
Dipyridamole	No additional risks known	Additional risks known	Additional risks known
Domperidone	No additional risks known	No additional risks known	Unsafe
Elbasvir/grazoprevir	No additional risks known	Unsafe	Unsafe
Enalapril	No additional risks known	Additional risks known	Unsafe
Eprosartan	No additional risks known	Additional risks known	Unsafe
Ezetemibe	No additional risks known	Unsafe	Unsafe
Felodipine	No additional risks known	No additional risks known	Unsafe
Fentanyl	Safe	Safe	No additional risks known

Fluvastatin	No additional risks known	No additional risks known	Unknown
Fosinopril	No additional risks known	Additional risks known	Unsafe
Gemfibrozil	No additional risks known	Unknown	Unknown
Interferon alfa-2a	Additional risks known	Unsafe	Unsafe
Interferon alfa-2b	Additional risks known	Unsafe	Unsafe
Irbesartan	No additional risks known	Additional risks known	Unsafe
Lercanidipine	Unknown	Unknown	Unsafe
Lisinopril	No additional risks known	Additional risks known	Unsafe
Lomitapide	Unknown	Unsafe	Unsafe
Losartan	No additional risks known	Additional risks known	Unsafe
Metoprolol	No additional risks known	No additional risks known	Unsafe
Mycophenolate mofetil	No additional risks known	No additional risks known	Unknown
Olmесartan	No additional risks known	Additional risks known	Unsafe
Ombitasvir/paritaprevir/ ritonavir	No additional risks known	Additional risks known	Unsafe
Omeprazole	No additional risks known	No additional risks known	Unsafe
Peginterferon alfa-2a	Additional risks known	Unsafe	Unsafe
Peginterferon alfa-2b	Additional risks known	Unsafe	Unsafe
Perindopril	No additional risks known	Additional risks known	Unsafe
Pethidine	No additional risks known	No additional risks known	Unknown
Prasugrel	No additional risks known	No additional risks known	Unknown
Pravastatin	No additional risks known	No additional risks known	Unknown
Quinapril	Unknown	Additional risks known	Unsafe
Rabeprazole	No additional risks known	No additional risks known	Unsafe
Ramipril	No additional risks known	Additional risks known	Unsafe
Repaglinide	Unknown	Additional risks known	Additional risks known
Ribavirin	No additional risks known	Additional risks known	Additional risks known
Rosuvastatin	No additional risks known	No additional risks known	Unknown

Simeprevir	No additional risks known	Unsafe	Unsafe
Simvastatin	Safe	Safe	Unknown
Sitagliptin	No additional risks known	No additional risks known	Unknown
Tapentadol	Unknown	Unknown	Unsafe
Telmisartan	No additional risks known	Additional risks known	Unsafe
Ticagrelor	No additional risks known	Unknown	Unknown
Tigecycline	No additional risks known	No additional risks known	Additional risks known
Trandolapril	Unknown	Additional risks known	Unsafe
Valsartan	No additional risks known	Additional risks known	Unsafe
Verapamil (IV) <sup>a</sup>	No additional risks known	No additional risks known	Unsafe
Verapamil (PO) <sup>a</sup>	No additional risks known	No additional risks known	Unsafe
Zofenopril	Unknown	Additional risks known	Unsafe

IV: intravenous, PO: per os.

a. Safety class of verapamil is similar for intravenous and oral administration, dosing advice is different.

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**Supplementary Table 2. Recommended dosing advice for 67 drugs when used in patients with liver cirrhosis.**

<b>Drug</b>	<b>Dosing advice</b>
Acenocoumarol	Recommended initial dosing: day 1: 4 mg or 3 mg; day 2: 2 mg; day 3: 1 mg; day 4: test INR
Acetylsalicylic acid	Use no more than the dose used for platelet aggregation inhibition
Amlodipine	CTP A: no dose adjustment needed CTP B: start with 50% of the normal dose <sup>a</sup> CTP C: start with 25% of the normal dose <sup>a</sup>
Benazepril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Bisoprolol	CTP A+B: no dose adjustment needed CTP C: use a maximum of 10 mg daily
Buprenorphine	CTP A: no dose adjustment needed CTP B+C: start with 50% of the normal dose <sup>a</sup>
Candesartan	CTP A+B: start with 4 mg once daily <sup>a</sup> CTP C: unsafe
Captopril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Carbasalate calcium	Use no more than the dose used for platelet aggregation inhibition
Carvedilol	CTP A: no dose adjustment needed CTP B: start with 50% of the normal dose <sup>a</sup> CTP C: start with 25% of the normal dose <sup>a</sup>
Clindamycin	CTP A: no dose adjustment needed CTP B+C: use a dosing interval of 8 hours
Dalteparin	Give twice daily if used in therapeutic dose
Dapagliflozin	CTP A+B: no dose adjustment needed CTP C: start with 5 mg, increase to a maximum of 10 mg once daily.
Diltiazem	start with 50% of the normal dose <sup>a</sup>
Domperidone	CTP A: no dose adjustment needed CTP B: use a third of the normal dose CTP C: unsafe
Enalapril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Enoxaparin	Give twice daily if used in therapeutic dose
Esomeprazole	CTP A+B: no dose adjustment needed CTP C: use a maximum of 20 mg once daily
Eprosartan	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Felodipine	CTP A+B: start with 50% of the normal dose <sup>a</sup> CTP C: unsafe

Fentanyl	start with 50% of the normal dose <sup>a</sup>
Fluvastatin	CTP A+B: start with 20 mg once daily <sup>a</sup> CTP C: unknown
Fosinopril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Glibenclamide	Start as low as possible <sup>a</sup>
Gliclazide	Start as low as possible <sup>a</sup>
Glimepiride	Start as low as possible <sup>a</sup>
Heparin	Aim at an aPTT 1.5-2.5 times prolonged
Hydromorphone (PO)	CTP A+B: start with 25% of the normal dose <sup>a</sup> CTP C: unknown
Irbesartan	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Labetalol (PO)	Start with 50% of the normal dose <sup>a</sup>
Lacidipine	Start with 2 mg once daily <sup>a</sup>
Lisinopril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Lomitapide	CTP A: start with 5 mg once daily, increase to a maximum of 40 mg per day CTP B+C: unsafe
Losartan	CTP A+B: start with 12.5 mg once daily <sup>a</sup> CTP C: unsafe
Metoclopramide	CTP A: no dose adjustment needed CTP B+C: use 50% of the normal dose <sup>a</sup>
Metoprolol	CTP A: no dose adjustment needed CTP B: start with a third of the normal dose <sup>a</sup> CTP C: unsafe
Morphine (PO)	CTP A+B: start with 50% of the normal dose <sup>a</sup> CTP C: start with 25% of the normal dose <sup>a</sup>
Morphine (IV)	CTP A: no dose adjustment needed CTP B+C: double the dosing interval <sup>a</sup>
Nadoparin	Give twice daily if used in therapeutic dose
Nifedipine	CTP A+B: start with 50% of the normal dose <sup>a</sup> CTP C: start with 50% of the normal dose and double the dosing interval <sup>a</sup>
Nimodipine (PO)	Start with 30 mg three times daily <sup>a</sup>
Omeprazole	CTP A+B: use a maximum of 20 mg once daily CTP C: unsafe
Olmесartan	CTP A: start with 10 mg once daily <sup>a</sup> CTP B: start with 10 mg once daily, increase to a maximum of 20 mg per day CTP C: unsafe
Oxycodone	CTP A+B: start with 50% of the normal dose <sup>a</sup> CTP C: start with 50% of the normal dose and double the dosing interval <sup>a</sup>
Perindopril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Phenprocoumon	Recommended initial dosing: day 1: 9 mg or 6 mg; day 2: 3 mg; day 3: 1.5 mg; day 4: test INR
Pioglitazone	Start with 15 mg once daily, increase to a maximum of 45 mg
Piritramide	Use a maximum of 10 mg at once
Pravastatin	CTP A+B: Start with 10 mg once daily <sup>a</sup> CTP C: unknown

Propranolol	Start with a maximum of 20 mg three times daily <sup>a</sup>
Quinapril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Rabeprazole	CTP A: start with 10 mg once daily, use a maximum of 20 mg per day CTP B: use a maximum of 10 mg per day CTP C: unsafe
Ramipril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Repaglinide	CTP A: Start with 50% of the normal dose <sup>a</sup> CTP B+C : Start with 50% of the normal dose, increase to a maximum of 4 mg per day
Rosuvastatin	CTP A+B: Start with 5 mg once daily <sup>a</sup> CTP C: unknown
Roxithromycin	CTP A+B: no dose adjustment needed CTP C: use 150 mg per day
Simvastatin	CTP A+B: Start with 20 mg once daily <sup>a</sup> CTP C: unknown
Tapentadol	CTP A+B: start with 50 mg three times daily or 50 mg retard once daily <sup>a</sup> CTP C: unsafe
Telmisartan	CTP A+B: start with 20 mg once daily, increase to a maximum of 40 mg per day <sup>a</sup> CTP C: unsafe
Tigecycline	CTP A+B: no dose adjustment needed CTP C: reduce maintenance dose to 25 mg twice daily
Tolbutamide	Start as low as possible <sup>a</sup>
Tramadol	CTP A: start with 50 mg every 12 hours <sup>a</sup> CTP B+C: start with 25 mg, increase to a maximum of 100 mg every 12 hours
Trandolopril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe
Valsartan	CTP A+B: start with 40 mg once daily, increase to a maximum of 80 mg per day CTP C: unsafe
Verapamil (PO)	CTP A+B: start with 40 mg twice daily and increase with a dosing interval of 12 hours CTP C: unsafe
Verapamil (IV)	CTP A+B: use a third of the normal maintenance dose CTP C: unsafe
Zofenopril	CTP A+B: start as low as possible <sup>a</sup> CTP C: unsafe

CTP: Child-Pugh class, IV: intravenous, PO: per os.

a. Increase the dose carefully according to clinical response and adverse drug reactions.