Famciclovir

Famciclovir + Probenecid

Probenecid is predicted to increase the exposure to penciclovir, the active metabolite of famciclovir, possibly resulting in increased adverse effects.

Evidence is limited and an interaction is not established. Consider an interaction as a possible cause if famciclovir adverse effects (such as diarrhoea, nausea, sweating and pruritus) occur.

Febuxostat

Febuxostat + Theophylline

Febuxostat is predicted to increase the exposure to theophylline, however febuxostat 80 mg daily had no effect on the pharmacokinetics of single-dose theophylline.

If both drugs are considered essential, check for signs of theophylline adverse effects (headache, nausea, tremor), monitoring theophylline concentrations and adjusting the dose accordingly. The UK manufacturer states that no special precautions are necessary when febuxostat 80 mg is given with theophylline.

Felbamate

Felbamate + Gabapentin

There is some evidence to suggest that the half-life of felbamate may be prolonged by gabapentin.

The clinical importance of this interaction is unknown, but be alert for the need to reduce the felbamate dose.
Felbamate

**Felbamate + Perampanel**

Felbamate possibly decreases perampanel concentrations. Until more is known, monitor perampanel efficacy and increase the dose if necessary.

**Felbamate + Phenobarbital**

Felbamate normally causes a moderate increase of about 25 to 30% in phenobarbital levels (derived from phenobarbital or primidone). Phenobarbital toxicity has occurred in one patient when felbamate was added. Warn the patient to monitor for indicators of phenobarbital toxicity (drowsiness, ataxia or dysarthria), and take levels if necessary.

**Felbamate + Phenytoin**

Felbamate causes a moderate increase in phenytoin levels. Felbamate levels are reduced by phenytoin but the importance of this is uncertain. It seems possible that fosphenytoin, which is a prodrug of phenytoin, will interact similarly. Warn the patient to monitor for indicators of phenytoin toxicity (blurred vision, nystagmus, ataxia or drowsiness). Take phenytoin levels and adjust the dose as necessary. The phenytoin dose may need to be reduced by up to 40%.

**Felbamate + Ulipristal**

The US manufacturer of ulipristal predicts that CYP3A4 inducers (they name felbamate) might decrease the exposure to ulipristal and reduce its efficacy. Felbamate is not an established CYP3A4 inducer and so a clinically relevant interaction with ulipristal would not be expected.

**Felbamate + Valproate**

Felbamate can raise valproate levels (by about 50% with a 2.4 g dose of felbamate), which may cause toxicity. Valproate may slightly decrease the clearance of felbamate. Monitor valproate levels if toxicity is suspected (indicators of valproate toxicity include nausea, vomiting and dizziness), some have suggested a 30 to 50% dose reduction may be needed. Be aware that the felbamate dose may need to be decreased.

**Fesoterodine**

**Fesoterodine + HIV-protease inhibitors**

Ketokonazole increases fesoterodine exposure about 2.5-fold by inhibiting CYP3A4. The
HIV-protease inhibitors inhibit CYP3A4 to varying extents, but are generally considered to be potent CYP3A4 inhibitors, and therefore they may be expected to interact similarly.

The manufacturers state that the dose of fesoterodine should be restricted to 4 mg daily with potent CYP3A4 inhibitors; however, note that they contraindicate the concurrent use of potent CYP3A4 inhibitors in patients with moderate to severe hepatic or renal impairment, and advise avoiding concurrent use in those with mild renal or hepatic impairment. Monitor for an increase in fesoterodine adverse effects (e.g. dry mouth, dizziness, insomnia), and consider reducing the fesoterodine dose if these become troublesome.

**Fesoterodine + Macrolides**

*Clarithromycin or Telithromycin*  
Ketoconazole increases fesoterodine exposure up to about 2.5-fold by inhibiting CYP3A4. Other potent CYP3A4 inhibitors (e.g. clarithromycin or telithromycin) are predicted to interact similarly.

The manufacturers state that the dose of fesoterodine should be restricted to 4 mg daily on concurrent use with potent CYP3A4 inhibitors such as clarithromycin or telithromycin; however, note that they contraindicate the concurrent use of potent CYP3A4 inhibitors in those with moderate to severe hepatic or renal impairment, and advise avoiding concurrent use in those with mild renal or hepatic impairment. It may be prudent to monitor for an increase in fesoterodine adverse effects (e.g. dry mouth, dizziness, insomnia), and consider reducing the fesoterodine dose if these become troublesome.

*Other macrolides*  
Fluconazole, a moderate CYP3A4 inhibitor, slightly increases the exposure to the active metabolite of fesoterodine, although an increase in some minor adverse effects, such as nausea and dizziness, occurred. Erythromycin would be expected to interact similarly.

No fesoterodine dose adjustment is necessary on concurrent use. Bear in mind the possibility of an interaction should an increase in adverse effects occur (e.g. dry mouth, dizziness, insomnia). Concurrent use should be avoided in patients with severe renal impairment, and a maximum fesoterodine dose of 4 mg daily given to those with mild to moderate renal impairment. Concurrent use should also be avoided in patients with moderate or severe hepatic impairment, and a maximum dose of fesoterodine 4 mg daily given to those with mild hepatic impairment.

**Fesoterodine + Phenobarbital**

Rifampicin reduces the levels of the active metabolite of fesoterodine by about 75%. Phenobarbital, and primidone, which is in part metabolised to phenobarbital, would be expected to interact similarly.

Concurrent use is not recommended by the UK manufacturer. However, the US manufacturer states that no fesoterodine dose adjustments are recommended. If both drugs are given it would be prudent to monitor for fesoterodine efficacy.
**Fesoterodine**

**Fesoterodine + Phenytoin**

Phenytoin, and fosphenytoin, a prodrug of phenytoin, would be expected to interact similarly.

Concurrent use is not recommended by the UK manufacturer. However, the US manufacturer states that no fesoterodine dose adjustments are recommended. If both drugs are given it would be prudent to monitor for fesoterodine efficacy.

**Fesoterodine + Rifampicin (Rifampin)**

Concurrent use is not recommended by the UK manufacturer. However, the US manufacturer states that no fesoterodine dose adjustments are recommended. If both drugs are given it would be prudent to monitor for fesoterodine efficacy.

**Fibrates**

**Fibrates + HIV-protease inhibitors**

Lopinavir boosted with ritonavir slightly decreases gemfibrozil exposure.

It seems possible that gemfibrozil efficacy will be decreased. Bear this possibility in mind on the concurrent use of these drugs.

**Fibrates + Montelukast**

Gemfibrozil moderately increases the exposure to montelukast

Monitor concurrent use for an increase in montelukast adverse effects (such as abdominal pain, headache; and hyperkinesia in young children) and reduce the montelukast dose, if necessary. Some have suggested that a dose reduction of 50 to 80% might be required.

**Fibrates + Statins**

The concurrent use of a statin and a fibrate increases the risks of muscle toxicity (e.g. myopathy or rhabdomyolysis). Clinically relevant pharmacokinetic interactions appear to occur between some statins and gemfibrozil, with gemfibrozil moderately increasing the exposure to lovastatin, pravastatin, and simvastatin. This increases the risk of muscle toxicity.

In general, the concurrent use of a statin and a fibrate should only be undertaken if the benefits of treatment outweigh the risks, with the lowest necessary doses of each drug given. Patients taking statins should be counselled regarding myopathy (e.g. report any unexplained muscle pain, tenderness, or weakness). This should be reinforced if they are also given a fibrate. Various dose adjustments are recommended on the concurrent use of certain statins and fibrates, as follows:
Atorvastatin – starting dose of 10 mg daily with a fibrate (UK advice), with alternatives to gemfibrozil considered.

Lovastatin – avoid gemfibrozil where possible, particularly in patients with compromised liver or renal function, unless the benefits outweigh the risks. A maximum of 20 mg daily with a starting dose of 5 mg daily is recommended with a fibrate (US advice).

Rosuvastatin – avoid gemfibrozil where possible, unless the benefits outweigh the risks. A starting dose of 5 mg daily (UK advice) and a maximum dose of 10 mg daily (US advice) is advised with gemfibrozil. Avoid 40 mg daily with any fibrate (UK advice).

Simvastatin – concurrent use with gemfibrozil is contraindicated. A maximum 10 mg daily is recommended with a fibrate (UK advice), except for fenofibrate, where no dose restrictions are deemed necessary.

In addition, the manufacturer of bezafibrate contraindicates the use of any statin if a number of conditions considered to be risk factors for myopathy (such as renal impairment and hyperthyroidism) are present.

Fibrates + Ursodeoxycholic acid (Ursodiol)

The concurrent use of fibrates is predicted to decrease the efficacy of ursodeoxycholic acid by increasing cholesterol elimination in the bile and thus encouraging gallstone formation.

The manufacturers do not recommend concurrent use.

Fibrates + Warfarin and related oral anticoagulants

The fibrates increase the effects of the coumarins and fatalities have resulted from this interaction. Most data is with the coumarin, although case reports suggest the indanediones may interact similarly. Gemfibrozil did not interact in a controlled study, although two cases of an interaction have been reported.

Evidence is not available for all combinations of fibrates and coumarins or indanediones, but it would seem prudent to expect them all to interact, to a greater or lesser extent. Coumarin and indanedione dose reductions may be needed to avoid the risk of bleeding. Monitor the INR and adjust the dose accordingly.

Finasteride

Finasteride + Herbal medicines or Dietary supplements

St John’s wort moderately reduces the exposure to finasteride.

It is possible that finasteride will be less effective in those taking St John’s wort.
Finasteride

Therefore it would seem prudent to bear the potential for reduced efficacy in mind, especially in patients taking finasteride for benign prostatic hyperplasia.

Finasteride + Testosterone

Testosterone is poorly bioavailable by the oral route, and is rapidly metabolised to dihydrotestosterone by 5-alpha reductase. By inhibiting this enzyme, finasteride reduces the formation of dihydrotestosterone and increases the exposure to oral testosterone.

Finasteride might be useful in increasing testosterone oral bioavailability for oral replacement therapy. No action needed.

Flecainide

Flecainide + H2-receptor antagonists

Cimetidine increases flecainide plasma concentrations.

The clinical importance of this interaction does not appear to have been assessed, but be alert for flecainide adverse effects (such as dizziness, nausea and tremor) and consider the need to reduce the flecainide dose, if cimetidine is added. The interaction is likely to be enhanced in the presence of renal impairment.

Flecainide + HIV-protease inhibitors

Ritonavir and tipranavir might increase the plasma concentration of flecainide. This increases the risk of arrhythmias and other adverse effects. Other HIV-protease inhibitors boosted with ritonavir are expected to interact similarly.

Concurrent use is generally contraindicated. If concurrent use is necessary, monitor carefully for flecainide adverse effects (such as dizziness, nausea or tremors) and adjust the flecainide dose if required.

Flecainide + Lacosamide

Dose-dependent prolongation of the PR interval may occur with lacosamide. The UK manufacturer therefore advises that lacosamide should be used with caution in patients taking class I antiarrhythmics, such as flecainide.

Be aware that ECG changes may occur on concurrent use.

Flecainide + Lumefantrine

The manufacturer of a preparation containing artemether and lumefantrine notes that in vitro lumefantrine significantly inhibits CYP2D6. They therefore contraindicate any drug that is metabolised by CYP2D6, and specifically name flecainide.

These contraindications seem unnecessarily restrictive, especially as flecainide is