

BOSENTAN and POSSIBLE DRUG INTERACTIONS (No 2,Jan 2005)

Background Bosentan is metabolised in the liver by Cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4 to 3 metabolites, one of which is thought to be active. It is then eliminated by biliary excretion with less than 3% of an oral dose being recovered in the urine. It also induces CYP2C9 and CYP3A4 (and poss. CYP2C19 and the P-glycoprotein) hence inducing the metabolism of other substrates of these enzymes. In addition it is also thought to inhibit the bile salt export pump. The potential for drug interactions is substantial. Bosentan induced elevation in liver aminotransferases is thought to be dose dependant and inhibition of CYP2C9 and/or CYP3A4 may increase the plasma concentration of Bosentan. The Summary of Product Characteristics (SmPC) for Bosentan states 'concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor should be avoided' and 'the possibility of altered efficacy of medicinal products metabolised by these enzymes should be considered'.

Bile Salt Export Pump Inhibitors

Glibenclamide*	Vitamin E	*SmPC recommends avoid
Ciclosporin*	Fexofenadine	
Rifampicin*		

Inhibitors CYP2C9

Fluconazole* -----

Amiodarone -----
 Atorvastatin -----
 Fluvastatin -----
 Cimetidine -----
 Miconazole -----
 Voriconazole -----
 Omeprazole (?)-----
 Fluoxetine (?)-----
 Sertraline (?)-----
 Paroxetine -----
 Sulfamethoxazole -----
 Trimethoprim -----
 Zafirlukast -----
 Capecitabine -----

Inhibitors CYP3A4

Fluconazole*

Glibenclamide*
Ciclosporin*
 Amiodarone -----
 Atorvastatin -----
 Cimetidine -----
 Isoniazid -----
 Miconazole -----
 Voriconazole -----
 Ketoconazole -----
 Itraconazole -----
 Omeprazole -----
 Fluoxetine -----
 Sertraline -----
 Fluvoxamine -----
 Clarithromycin -----
 Erythromycin -----
 Metronidazole -----
 Diltiazem -----
 Nifedipine -----
 Verapamil -----
 Quinine -----
 Nefazodone -----
 Grapefruit Juice -----
 Reboxetine -----

Metabolism Induced

Glibenclamide*
Oral contraceptives (1)
Warfarin (2)
Simvastatin (3)
Digoxin

Sildenafil

OMISSION FROM THIS TABLE DOES NOT IMPLY THAT THE COMBINATION IS SAFE. AS KNOWLEDGE PROGRESSES FURTHER ADDITIONS ARE LIKELY.

- (1) Additional or alternative reliable method of contraception advised
- (2) Intensified monitoring of INR recommended
- (3) Monitor cholesterol levels and adjust dose if necessary