

SITAXENTAN and POSSIBLE DRUG INTERACTIONS (Jan 2007)

Background Sitaxentan is metabolised in the liver by Cytochrome P450 (CYP) isoenzymes CYP2C9 (major pathway) and CYP3A4 (minor pathway). Approximately half of an oral dose is excreted in the urine with the remainder eliminated in the faeces. Although there is potential for interaction with CYP2C9 and CYP3A4 inhibitors studies to date have indicated only minor changes to Sitaxentan levels. Inducers of these enzymes are likely to increase the clearance of Sitaxentan. Sitaxentan is a moderate inhibitor of CYP2C9 and a weak inhibitor of CYP2C19, CYP3A4 and CYP2C8. It therefore has potential to block the metabolism of drugs that are substrates of these enzymes particularly CYP2C9. It is thought that Sitaxentan is a substrate of the Organic Anion Transporting Polypeptide (OATP) which transports it into hepatocytes prior to metabolism. Blockage of this transfer is a possible explanation of the profound interaction (6fold increase) with Ciclosporin and the SmPC advises caution when used with more potent OATP inhibitors.

Contraindication (SmPC)
Ciclosporin*

Substrates CYP2C9

S- Warfarin

Sildenafil(28%↑)

Diclofenac

Ibuprofen

Meloxicam

Naproxen

Piroxicam

Flurbiprofen

Glipizide

Tolbutamide

Losartan

Irbesartan

Amitriptyline

Fluoxetine

Phenytoin

Rosiglitazone

Tamoxifen

Trimethoprim

Zafirlukast

When initiating Sitaxentan in patients already taking Warfarin it is recommended that the Warfarin dose is halved (STRIDE-2 study mean Warfarin dose 40% lower). If starting Warfarin in a patient taking Sitaxentan then start at the lowest available dose (usually 1mg) and titrate up in 1mg increments (mean STRIDE-2 dose 2.1mg daily). **In all cases careful monitoring of INR is required with only small incremental changes in Warfarin dose).**

Potential OATP inhibitors

Ciclosporin	Imipramine
Simvastatin	Warfarin
Lovastatin	Quinidine
Pravastatin	Verapamil
Glibenclamide	Digoxin
Tolbutamide	Quinine
Rifampicin	Nelfinavir
Ibuprofen	Ritonavir
Indomethacin	Saquinavir
Ketoconazole	

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