We have some trouble with special characters and displaying monographs. 22.09.2018

ATC code:
J05AE03

Classification:
P - Porphyrinogenic

Substance:
Ritonavir

Important information:
Very common side effects of ritonavir are abdominal pains, nausea, diarrhoea, vomiting and back pains. These can be confused with an acute porphyric attack and may potentially be porphyrinogenic if leading to a decrease in carbohydrate intake.

Rationale for risk classification:
Ritonavir is a potent mechanism-based inhibitor of CYP3A4. It is also found to be an activator of hPXR and an inducer of several CYP450 enzymes, i.e. CYP1A2, 2B6, 2C9, 2C19 and 3A4. There is one clinical report describing an acute porphyric attack precipitated by ritonavir. Since the drug is both a strong mechanism-based inhibitor of CYP3A4 and a multi-inducer it is classified as porphyrinogenic.

Chemical description:
n-carbamoyl alpha amino acid

Therapeutic characteristics:
Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Low dose ritonavir is often used as a pharmacokinetic enhancer of other protease inhibitors, such as lopinavir, fosamprenavir and tipranavir. Elimination half-life is 3-5 hours.

It is administered orally.

Side effects or other pharmacodynamic effects of relevance to acute porphyria:
Very common adverse reactions of ritonavir are abdominal pains, nausea, diarrhoea, vomiting and back pains. Other common side effects are insomnia, anxiety, confusion, seizure and fever. These side effects can be confused with an acute porphyric attack and may potentially be porphyrinogenic if leading to a decrease in carbohydrate intake.

Metabolism and pharmacokinetics:
Ritonavir is mainly metabolized by CYP3A4 and to a lesser extent by CYP2D6 (SPC). About 86 % of a dose is eliminated through the faeces and 34 % as unchanged drug (SPC).

Ritonavir is a potent mechanism-based inhibitor of CYP3A4 in vitro (Ernest 2005, Rock 2014). The mechanism of CYP3A4 inactivation is suspected to occur via MI-complex formation with CYP3A4 (Ernest 2005), and/or irreversible covalent binding of ritonavir to CYP3A4 apoprotein (Rock 2014), and/or due to heme destruction accompanied by formation of a heme-protein adduct (Lin 2013). Ritonavir is listed as a strong inhibitor of CYP3A4 (FDA). Co-administration of ritonavir/saqinavir and simvastatin (a CYP3A4 substrate) resulted in a 31.6-fold increase in the AUC of simvastatin (Lexi-Interact). Ritonavir is found to be a reversible inhibitor of CYP2D6 in vitro (von Moltke 1998a) and it is listed as a weak inhibitor of CYP2D6 (FDA). Ritonavir was also found to be a mechanism-based inhibitor of CYP2B6 in vitro (Lin 2013).

Ritonavir is reported to be an activator of hPXR (Pelkonen 2008, Sinz 2006), and an inducer of CYP3A4 (Ouellet 1998), CYP1A2, 2B6, 2C9 and 2C19 (Kirby 2011). An in vivo study found that ritonavir/lopinavir induced CYP1A2, 2C9 and 2C19 (Yeh 2006). Co-administration of darunavir/ritonavir and ethinyl estradiol resulted in a 44 % decrease in the AUC of ethinyl oestradiol and this is suspected to be due to CYP3A4 induction (interactionsdatabasen.dk, Lexi-interact, Ouellet 1998). Co-administration of ritonavir 600 mg twice daily and bupropion (a CYP2B6 substrate) for 8 days resulted in a 66 % decrease in AUC of bupropion, due to induction of CYP2B6 (Kharasch 2008). This is in contrast to in vitro data suggesting that ritonavir was an inhibitor of CYP2B6 (Lin 2013).

**Published clinical experience:**

A published case report describes an acute porphyric attack in a female AIP patient, most likely triggered by ritonavir and atazanavir (Bharti 2016).

**References:**


Lexi-Interact in UpToDate. substansnavn: Drug interaction program.


Yeh RF, Gaver VE, et al. Lopinavir/ritonavir induces the hepatic activity of cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP1A2 but inhibits the hepatic and intestinal activity of CYP3A as measured by a phenotyping drug cocktail in healthy volunteers. J Acquir Immune Defic Syndr. 2006 May;42(1):52-60.