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ATC code:
J05AR09

Classification:
PRP - Probably porphyrinogenic

Substance:
Emtricitabine, tenofovir disoproxil, elvitegravir and cobicistat

Important information:
Side effects like nausea, vomiting diarrhoea may potentially be porphyrinogenic through reduction in carbohydrate intake.

Rationale for risk classification:
This combination product contains four substances: Emtricitabine (ATC-code: J05AF09), tenofovir disoproxil (ATC-code J05AF07), cobicistat (ATC-code: V03AX03) and elvitegravir (ATC-code: J05AX11). Cobicistat is a potent mechanism-based inhibitor of CYP3A4 and is thus probably porphyrinogenic. The combination is therefore classified as probably porphyrinogenic.

Chemical description:
Emtricitabine belongs to a class known as 3’-thia pyrimidine nucleosides
Tenofovir belongs to the class 6-aminopurines
Cobicistat is a ritonavir derivative
Elvitegravir is a dihydroquinoline carboxylic acid derivative

Therapeutic characteristics:
Emtricitabine and tenofovir are nucleoside reverse transcriptase inhibitors (NRTIs). Elvitegravir is a HIV-1 integrase strand transfer inhibitor (ISTI) and cobicistat is a pharmacokinetic enhancer of CYP3A4 substrates. The combination product is indicated for the treatment of HIV-1 infection in adults. It is administered orally.

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

Metabolism and pharmacokinetics:
Emtricitabine is not metabolized by CYP450 enzymes and is not an inducer or an inhibitor of CYP450 enzymes (SPC). Emtricitabine is classified as probably not porphyrinogenic (see monograph, ATC-code: J05AF09).

Tenofovir disoproxil is not metabolized by CYP450 enzymes and is not an inducer or an inhibitor of CYP450 enzymes (SPC). Tenofovir disoproxil is classified as probably not porphyrinogenic (see monograph, ATC-code: J05AF07).

Cobicistat is mainly metabolized by CYP3A4, with minor contribution by CYP2D6 (SPC). It is a strong mechanism-based inhibitor of CYP3A4 and is used as a pharmacokinetic enhancer to increase exposure of elvitegravir (SPC, Xu 2010). When cobicistat (200 mg) was co-administered with midazolam (a CYP3A4 substrate) a 95 % reduction was seen in the clearance of midazolam (Larson 2014). It is also a weak inhibitor of CYP2D6. Cobicistat is not suspected to be an inhibitor of CYP1A2, 2B6, 2C8, 2C9 or 2C19, and is not expected to induce CYP3A4, 1A2, 2B6, 2C8, 2C9 and 2C19 (SPC).

Elvitegravir is metabolized by CYP3A4 with further glucuronidation (SPC). It is reported to be a weak inducer of CYP2C9 and has been found to increase metabolism of warfarin resulting in sub therapeutic INR values (Good 2015). It is also suspected to be an inducer of CYP1A2, 2C9, 2C19 and 3A4 in vitro (SPC), but there are no clinically relevant drug-drug interactions where elvitegravir is the perpetrator (Ramanathan 2011). Co-administration with elvitegravir/cobicistat and ethinyl estradiol/norgestimate resulted in a 25 % decrease in AUC of ethinyl estradiol, which may be due to elvitegravir inducing CYP2C9, and a 126 % increase in the AUC of norgestimate, which may be due to cobicistat inhibiting CYP3A4 (SPC, Lexi-interact).

**References:**


http://www.medicines.org.uk/EMC/. (Last edition: 01.05.2015).