Enzalutamide + Gemfibrozil MFB 1186

Onderbouwend	Stof	Effect	Code
Gibbons JA. Clin Pharmacokinet 2015;54:1057-69.	enzalutamide + gemfibrozil	↑ AUC enzalutamide plus actieve metaboliet 2.2x Regime: enzalutamide 160 mg 1-malig op dag 1 en 4, gemfibrozil 600 mg 2dd op dag 1-21; 13 vrijwilligers	3A
SPC Xtandi EPAR Xtandi M1: inactive metaboliet M2: actieve metaboliet	enzalutamide + gemfibrozil	- enzalutamide: ↑ AUC met 326%, ↓Cmax met 18% - som ongebonden enzalutamide plus actieve metaboliet: ↑ AUC met 77%, ↓ Cmax met 19%. Regime: gemfibrozil 600 mg 2dd gedurende 21 dagen en op dag 4 enzalutamide 160 mg 1-malig, gezonde mannelijke proefpersonen (studie 9785-CL-0006). After 18 days, when gemfibrozil administration was discontinued, the elimination rate of enzalutamide increased, and the plasma level of M2 started to rise. Due to the concern that gemfibrozil administration was too short to mirror the worst-case effect of a CYP2C8 inhibitor, the interaction was quantified using compartmental modelling and simulation to predict the change with no discontinuation of gemfibrozil. The result suggested a T/R ratio of 4.26. The T/R when comparing AUC for the first 18 days with noncompartmental methods was 2.53 and no AUCinf was calculated with non-compartmental methods. Gemfibrozil caused an increase in M1 (AUC 2.7-fold higher) whereas the levels of M2 decreased by 25%. Thus the effect of CYP2C8 inhibition on active moiety (parent+M2) is lower (2.2-fold) compared to the effect of enzalutamide itself (4.3-fold).	2A

Overig	Stof	Effect
SPC Xtandi	enzalutamide + CYP2C8-remmers	combinatie met sterke CYP2C8-remmers (bijv. gemfibrozil) van vermijden of met voorzichtigheid; bij combinatie dosis verlagen naar 80 mg 1dd (normaal 160 mg 1dd). CYP2C8 speelt een belangrijke rol bij de eliminatie van enzalutamide en de vorming van de actieve metaboliet. Overdosis: hoger risico op insulten.
EPAR Xtandi MTD: maximum tolerated dose	enzalutamide	p. 43 ev - Study S-3100-1-01: dose-escalation study, the MTD was determined to be 240 mg/day, based upon the occurrence of dose-limiting toxicities as well as adverse events of fatigue leading to dose reductions at higher doses. During this study 5 dose-limiting toxicities were observed in 4 patients: seizure (n=3, doses 360 - 480 mg - 600 mg/day) and rash (n=1 at 600 mg/day). Dose-dependent increase in fatigue leading to dose reduction: no incidence at 150 mg/day, 2.9% incidence at 240 mg/day, 7.5% incidence at 360 mg/day, and 20.0% incidence at 480 mg/day.

Opmerkingen
Werkgroep Interacties met oncologische middelen: 'heroverweeg indicatie gemfibrozil'→ vermijden.
PubMed: enzalutamide + gemfibrozil, drug interaction, of rifampicine: niets.
Stockley, Hansten, niet in Hansten PhD ea. The top 100 Drug Interactions. 2013 Edition: --

Risicogroep	

	Interactie	Actie	Datum
Beslissing WG OncoIA	Ja	Ja	27 januari 2016