Talazoparib + Enzalutamide M8472

Onderbouwend	Stof	Effect	Code
SPC Talzenna	talazoparib + enzalutamide	de blootstelling aan talazoparib is ongeveer 2x zo groot bij gelijktijdige toediening met enzalutamide 160 mg; de steady-state Cmin talazoparib bij 0.5 mg 1dd icm enzalutamide is ong. dezelfde als bij 1 mg 1dd zonder enzalutamide. Het interactie-effect van andere doses dan 160 mg enzalutamide op talazoparib is niet gekwantificeerd.	2A

Overig	Stof	Effect
SPC Talzenna	talazoparib icm enzalutamide	talazoparib 0.5 mg 1dd is geregistreerd icm enzalutamide bij gemetastaseerde castratieresistente prostaatkanker (nieuwe indicatie) → bij mammacarcinoom is dit 1 mg 1dd, zonder enzalutamide
EPAR Talzenna 09 November 2023 https://www.ema.europa.eu/en/documents/variation-report/talzenna-epar-public-assessment-report_en.pdf E = enzalutamide	talazoparib icm enzalutamide	p.33 When talazoparib is co-administered with E, exposure increases approximately 2-fold compared to monotherapy. The increase in talazoparib exposure may be due to inhibition of P-gp by E and its N-desmethyl metabolite in the intestine (increasing talazoparib bioavailability) and/or the renal tubules (reducing talazoparib elimination). It is likely that P-gp-inhibition effect of E plays an important role in increasing the absorption and thereby the exposure of talazoparib. However, the effect of E on talazoparib exposure is larger compared to P-gp inhibitor itraconazole indicating that other factors contribute to the interaction. Moreover, CL/F is decreased for the combination treatment compared to monotherapy suggesting renal P-gp-inhibition as well. In vitro data indicate that E may be an inhibitor of the efflux transporter P-gp. Also, a DDI study with probe P-gp substrate digoxin before and concomitantly with E increased AUC by 33% and Cmax by 17%.
EPAR Talzenna 09 November 2023 https://www.ema.europa.eu/en/documents/variation-report/talzenna-epar-public-assessment-report_en.pdf mCRPC = metastatic Castration Resistant Prostate Cancer	talazoparib + enzalutamide	The Applicant has submitted a grouped application, to seek approval for a new indication of oral combination treatment with talazoparib 0.5 mg QD + E 160 mg QD in mCRPC regardless of HRR-mutation status and extension with a new capsule strength (0.1 mg) for dose reduction measures. The reason for the lower dose of talazoparib in mCRPC compared to the previous approved dose in breast cancer is a drug-drug interaction between talazoparib and E, leading to increased talazoparib exposure. p.25 The first participants enrolled into Part 1 initially received talazoparib 1 mg QD in combination with E, based on the monotherapy dose used for breast cancer patients. E was administered at the labelled mCRPC dose of 160 mg QD. Safety data from the initial 13 participants enrolled to Part 1 showed higher than expected Grade 3 haematological toxicities likely due to an observed ~2-fold increase in talazoparib exposure with the combination regimen when compared to historical monotherapy PK data. Talazoparib dose was reduced from 1 mg QD to 0.5 mg QD for participants continuing to receive talazoparib in combination with E in Part 1, and a further 6 participants were enrolled at this lower starting dose. Part 1 data indicated that reducing the talazoparib dose to 0.5 mg QD in combination with E was expected to account for the observed DDI and maintain similar talazoparib exposure to that achieved with 1 mg QD monotherapy with an acceptable safety profile.

Opmerkingen
Werkgroep Interacties Oncologische middelen: actie Nee, is therapeutische combinatie.
Nieuwe indicatie talazoparib: prostaatkanker, icm enzalutamide, dosis talazoparib 0.5 mg 1dd. Bij mammacarcinoom is dit 1 mg 1dd, zonder enzalutamide. Talazoparib wordt getransporteerd door P-gp. Enzalutamide remt P-gp.

Stockley online feb 2024: moderate (enzalutamide moderately increases the exposure to talazoparib), adjust (when given with enzalutamide for prostate cancer, use a starting dose of talazoparib 0.5 mg once daily).

PubMed: niets

Risicofactoren	
Mitigerende factoren	

	Interactie	**Actie**	**Datum**
Beslissing WG OncoIA	Ja	Nee	2 oktober 2024