YONDELIS® (trabectedin)
Drug Interactions of YONDELIS – General

SUMMARY

- Cytochrome P450 3A (CYP3A) is the predominant CYP enzyme responsible for the hepatic metabolism of YONDELIS. YONDELIS was extensively metabolized with negligible unchanged drug in urine and feces following administration of YONDELIS to humans.[1]
- Avoid using strong CYP3A inhibitors (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) in patients taking YONDELIS. If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the YONDELIS infusion, and discontinue it the day prior to the next YONDELIS infusion.[1]
- Coadministration of multiple doses of ketoconazole (200 mg twice daily for 7.5 days), a strong CYP3A inhibitor, with a single dose of YONDELIS (0.58 mg/m^2) on day 1 increased YONDELIS dose-normalized area under the plasma concentration-time curve (AUC) by 66% and maximum plasma concentration (C_{max}) by 22% compared to a single YONDELIS dose (1.3 mg/m^2) given alone.[1,2]
- Avoid using strong CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) in patients taking YONDELIS.[1]
- Coadministration of multiple doses of rifampin (600 mg daily for 6 days), a strong CYP3A inducer, with a single YONDELIS dose (1.3 mg/m^2) on day 6 decreased YONDELIS AUC by 31% and C_{max} by 21% compared to a single YONDELIS dose (1.3 mg/m^2) given alone.[1,2]
- In vitro, YONDELIS has limited inhibition or induction potential of major CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4).[1]
- No substantial pharmacokinetic (PK) interactions were reported in combination studies with YONDELIS and cytotoxic agents (i.e., carboplatin, cisplatin, docetaxel, doxorubicin/pegylated liposomal doxorubicin, gemcitabine, paclitaxel).[3-11]
- Please refer to the DRUG INTERACTIONS and CLINICAL PHARMACOLOGY sections of the full Prescribing Information.

CLINICAL DATA

PK Drug-Drug Interactions of YONDELIS-Based Combinations

Table: PK YONDELIS Drug-Drug Interaction Studies summarizes PK YONDELIS drug-drug interaction studies. Please refer to the respective publications for additional information on these studies.

PK YONDELIS Drug-Drug Interaction Studies

Study	Intervention	PK Results
Strong Inhibitor/Inducer of CYP3A4		
Rifampin (CYP3A4 inducer), Ketoconazole (CYP3A4 inhibitor)		
Two phase 1/2a, randomized, open-label, single-dose, 2-way crossover studies[2] (rifampin, N=12) ketoconazole, (N=8)	Rifampin: Randomized 1:1 to (1) YONDELIS (1.3 mg/m^2 3-hr IV infusion) coadministered with rifampin (600 mg/day, 6 days), followed by YONDELIS alone (1.3 mg/m^2 3-hr IV infusion) OR (2) YONDELIS alone followed by YONDELIS and rifampin coadministration	Rifampin: Systemic exposure of YONDELIS was decreased with rifampin coadministration (C_{max}, 22% and AUC_{last}, 31%); this correlated with increased clearance (39.6-59.8 L/h) and thus, shorter half-life
	Ketoconazole: (Part A; n=4) ketoconazole (200 mg BID, 6 doses) with YONDELIS (0.2 mg/m^2, 3-hr IV	Ketoconazole: Systemic exposure of YONDELIS was increased with ketoconazole coadministration

	infusion) followed by YONDELIS alone (1.3 mg/m^2, 3-hr IV infusion). (Part B; n=8) randomized 1:1 to (1) YONDELIS (0.58 mg/m^2, 3-hr IV infusion) and ketoconazole (200 mg BID, 15 doses), followed by YONDELIS alone (1.3 mg/m^2, 3-hr IV infusion) OR (2) YONDELIS alone followed by YONDELIS and ketoconazole coadministration	(C_{max}, 22% and AUC_{last}, 66%); this correlated with decreased clearance (20.3-12.0 L/h)
Cytotoxic Agents		
Docetaxel		
Phase 1 study[3] (N=49)	Docetaxel (60 or 75 mg/m^2; 1-hr IV infusion) given on day 1 of a 21-day cycle in combination with escalating doses of YONDELIS (0.4-1.3 mg/m^2 by 3-hr IV infusion, 1 hr after docetaxel)	PK for YONDELIS plus docetaxel were similar to those previously reported for the agents administered alone
Carboplatin		
Phase 1 study[4] (N=44)	Carboplatin-pretreated patients received carboplatin AUC 4 (group 1) and carboplatin-naïve patients received carboplatin AUC 5 (group 2) as a 1-hr IV infusion, followed by YONDELIS (0.5-1.2 mg/m^2 over 3 hr) Q3W	No significant PK drug-drug interaction was observed
Paclitaxel		
Phase 1 study[5] (N=27)	Cycle 1: paclitaxel was administered 8 days before YONDELIS (day -7); Subsequent cycles: paclitaxel (80-120 mg/m^2; 1-hr IV infusion) administered on day 1, 24 hours before start of YONDELIS (0.525-0.775 mg/m^2; 3-hr IV infusion) Q2W	Relevant drug-drug PK interactions between paclitaxel and YONDELIS were not identified
Gemcitabine		
Phase 1 study[6] (N=15)	Gemcitabine (800 or 1000 mg/m^2) followed by YONDELIS (0.3-0.58 mg/m^2) administered at one dose level below MTD	PK were not substantially altered with concomitant administration
Cisplatin		
Phase 1 study[7] (N=49)	• In the DFP, YONDELIS was administered as 3-hr infusion in escalating doses in 100 mcg/m^2 increments up to the MTD, with fixed-dose cisplatin 40 mg/m^2 • In the ERDP, YONDELIS administered with corticosteroids as a 3-hr infusion and cisplatin as a 30-min infusion	No PK interaction was observed
Phase 1 study[8] (N=12)	Fixed-dose cisplatin (75 mg/m^2 1-hr IV infusion), followed by YONDELIS (0.60 or 0.75 mg/m^2 3-hr IV	A PK interaction between YONDELIS and cisplatin was observed, leading to increased plasma exposure of

	infusion), both administered on day 1 Q3W	YONDELIS in the first 48 hr, lower platinum clearance, and longer half-life
Doxorubicin/PLD		
Phase 1 study[9] (N=41)	Doxorubicin 60 mg/m^2 (10- to 15-min IV infusion) followed by YONDELIS 0.9-1.3 mg/m^2 (3-hr IV infusion) on day 1 of a 3-week cycle	PK was not substantially altered with concomitant administration
Phase 1 study[10] (N=38)	Doxorubicin 60 mg/m^2 and YONDELIS at escalating doses from 600 to 800 mcg/m^2	No PK interaction between the 2 drugs was observed
Phase 1 study[11] (N=36)	1-hr PLD (30 mg/m^2) IV infusion followed immediately by 1 of 6 YONDELIS doses (0.4-1.3 mg/m^2) infused IV over 3 hr, repeated every 21 days	PK was not substantially altered with concomitant administration

Abbreviations: AUC, area under the plasma concentration-time curve; AUC_{last}, area under the plasma concentration-time curve from time zero to the last quantifiable concentration; BID, twice daily; C_{max}, maximum plasma concentration; CYP3A4, cytochrome P450 3A4; DFP, dose-finding phase; ERDP, expansion-of-recommended-dose phase; hr, hour(s); IV, intravenous; min, minute(s); MTD, maximum tolerated dose; PK, pharmacokinetics; PLD, pegylated liposomal doxorubicin; Q3W, every 3 weeks.

OTHER RELEVANT LITERATURE

Rhabdomyolysis was reported in a case of a drug-herbal interaction between YONDELIS and Chokeberry (*Aronia melanocarpa*) in a 56-year-old patient with retroperitoneal liposarcoma (LPS).[12] The pharmacokinetic interactions of YONDELIS in combination with olaparib has also been evaluated.[13]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 21 October 2024.

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