SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
Use of SYMTUZA in Patients with Renal Impairment

SUMMARY

- SYMTUZA should not be initiated in patients who have an estimated glomerular filtration rate according to the Cockcroft-Gault formula for creatinine clearance ($eGFR_{CG}$) below 30 mL/min.[1]
- SYMTUZA should be discontinued in patients with $eGFR_{CG}$ that declines below 30 mL/min during treatment.[1]
- No dosage adjustment of SYMTUZA is required in patients with an $eGFR_{CG}$ of 30 mL/min or greater.[1]
- Due to extensive protein binding, it is unlikely that darunavir (DRV) or cobicistat (COBI) would be removed by hemodialysis (HD) or peritoneal dialysis (PD).[1]
- Emtricitabine (FTC) can be removed by HD, which removes approximately 30% of the dose over a 3 hour dialysis period starting within 1.5 hours of FTC dosing.[1]
- Tenofovir (TFV) is removed by HD with an extraction coefficient of approximately 54%.[1]
- It is not known if FTC or TFV can be removed by PD.[1]
- There are no studies conducted with the single-tablet regimen (STR) SYMTUZA in patients undergoing HD or PD.
- A case report of a patient undergoing HD who was receiving DRV 800 mg + COBI 150 mg QD found no significant difference in trough levels on days with and without HD.[2]
- The pharmacokinetics (PK) of the single-tablet regimen (STR) elvitegravir (EVG) 150 mg/COBI 150 mg/FTC 200 mg/tenofovir alafenamide (TAF) 10 mg (which contains 3 of the 4 components of SYMTUZA) was evaluated in adult patients with mild or moderate renal impairment or end-stage renal disease (ESRD) receiving HD.[3, 4]
    - In both patient populations, the PK of COBI and TAF were consistent with historical data in HIV-infected patients with normal renal function.
    - Increases in both FTC and TFV exposures were observed, but no increase in adverse effects was reported.

CLINICAL STUDIES WITH SYMTUZA

- The phase 3 registrational trials AMBER and EMERALD included 202 patients with estimated glomerular filtration rate (eGFR) 70 to <90 mL/min, 55 patients with eGFR 50 to <70 mL/min, and 3 patients with eGFR <50 mL/min who received SYMTUZA. The data from these subjects did not suggest any safety concerns.[5]

CLINICAL STUDIES WITH COMPONENTS OF SYMTUZA

Kobayashi et al (2021)[2] described in a case report from Japan the PK of DRV and COBI in a male patient in his 40s who was undergoing HD.

- The patient was receiving DRV 800 mg + COBI 150 mg + doravirine 100 mg once daily after breakfast. Drug concentrations for PK analysis were obtained on days 47, 54, and 82.
- Drug concentrations were measured at 4 timepoints:
    - A) trough on the day of HD
    - B) before HD (1 hour post-dose)
    - C) after HD (5 hours post-dose)
    - D) trough on the day after HD
- Data for DRV and COBI are presented in Table: PK of DRV and COBI Before and After Hemodialysis.
- Trough concentrations of DRV and COBI did not differ significantly on days with and without HD (P=0.44 and P=0.96, respectively).

PK of DRV and COBI Before and After Hemodialysis[2]

Drug	Concentration, Median (SD) in nM			
	Trough (day of HD)	Before HD	After HD	Trough (day after HD)
DRV	9,528 (2,101)	6,657 (1,715)	27,265 (6,976)	9,552 (1,575)
COBI	99 (28)	40 (8)	1826 (338)	121 (23)

Abbreviations: COBI, cobicistat; DRV, darunavir; HD, hemodialysis; PK, pharmacokinetics; SD, standard deviation.

Data from STR EVG/COBI/FTC/TAF Studies

- The PK of COBI, FTC, and TFV were evaluated in studies using the STR EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg in virologically suppressed HIV-1 infected adult patients with mild or moderate renal impairment (estimated CrCL between 30-69 mL/min by Cockcroft-Gault method), and in patients with ESRD (estimated CrCL of less than 15 mL per minute by Cockcroft-Gault method) receiving chronic HD who were enrolled in 2 respective open-label trials, Gilead study GS-US-292-0112 and Gilead study GS-US-292-1825.[3, 4]
  - In both patient populations, the PK of COBI and TAF were consistent with historical data in HIV-infected patients with normal renal function.[3, 4]
  - However, the PK of FTC and TFV were affected (see Table: PK of FTC and TFV in Adults with Normal Renal Function Compared to Patients with Renal Impairment and Patients with ESRD Receiving Chronic Hemodialysis).[3, 4]
  - Increases in FTC and TFV exposures were observed in patients with mild-moderate renal impairment.[3]
    - A comparison of FTC adverse reactions performed by baseline CrCL found no significant differences existed.
    - Exposure to TFV in patients with mild-moderate renal impairment was higher than historical data in patients with normal renal function, but was below that reported in patients receiving tenofovir disoproxil fumarate (TDF)-containing regimens.
  - Increases in FTC and TFV exposures were observed in patients undergoing HD, but the overall safety profile was not affected.[4]
    - TFV exposure was less than that achieved in HD patients receiving TDF.

PK of FTC and TFV in Adults with Normal Renal Function Compared to Patients with Mild-Moderate Renal Impairment and Patients with ESRD Receiving Chronic Hemodialysis[3, 4]

Drug	AUC_{tau} (mcg•h/mL), Mean (%CV)		
	Normal Renal Function[4] (n=19) [a,b]	CrCL 30-69 mL/min[3] (n=30) [a,c]	CrCL <15 mL/min[4] (n=12) [a,d]
FTC	11.7 (17)	21.0 (26)	62.9 (48)[e]
TFV	0.33 (15)	0.55 (32)	8.72 (39)[f]

Abbreviations: CrCL, creatinine clearance; CV, coefficient of variation; ESRD, end-stage renal disease; FTC, emtrictabine; PK, pharmacokinetics; TFV, tenofovir.
[a]CrCL estimated by Cockcroft-Gault method.
[b]From a Phase 2 study in adult HIV patients with normal renal function.
[c]Study GS-US-292-112; [d]Study GS-US-292-1825; PK assessed prior to hemodialysis following 3 consecutive daily doses of a single-tablet regimen containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
[e]n=11; [f]n=10.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 07 July 2023.

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