What are the pharmacokinetic and pharmacodynamic profiles for Verzenio® (abemaciclib)?

The pharmacokinetics (PK) of abemaciclib were characterized in patients with solid tumors, including breast cancer, and in healthy subjects.[1]

Following single and repeated twice daily dosing of 50 mg (0.3 times the approved recommended 150 mg dosage) to 200 mg of abemaciclib, the increase in plasma exposure (area under the curve [AUC]) and maximum concentration (C_{max}) was approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and the estimated geometric mean accumulation ratio was 2.3 (50% coefficient of variation [CV]) and 3.2 (59% CV) based on C_{max} and AUC, respectively.[1]

ABSORPTION

The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% (19% CV). Abemaciclib has a median time of C_{max} (T_{max}) of 8.0 hours (range: 4.1-24.0 hours).[1]

DISTRIBUTION

In vitro, abemaciclib was bound to human plasma proteins, serum albumin, and alpha-1-acid glycoprotein in a concentration independent manner from 152 ng/mL to 5066 ng/mL.[1]

In a clinical study, the mean (standard deviation [SD]) bound fraction was

- 96.3% (1.1) for abemaciclib
- 93.4% (1.3) for M2
- 96.8% (0.8) for M18, and
- 97.8% (0.6) for M20.[1]

The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV).[1]

In patients with advanced cancer, including breast cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations.[1]

ELIMINATION

The geometric mean hepatic clearance of abemaciclib in patients was 26.0 L/h (51% CV), and the mean plasma elimination half-life ($t_{1/2}$) for abemaciclib in patients was 18.3 hours (72% CV).[1]

Metabolism

Hepatic metabolism is the main route of clearance for abemaciclib.[1]

Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4.[1]

The major metabolism pathway is formation of N-desethylabemaciclib (M2).[1]

Additional metabolites include

- hydroxyabemaciclib (M20)
- hydroxy-N-desethylabemaciclib (M18), and
- an oxidative metabolite (M1).[1]

Of these metabolites, M2, M18, and M20 are equipotent to abemaciclib and their AUCs accounted for 25%, 13%, and 26% of the total circulating analytes in plasma, respectively.[1]

Excretion

After a single oral dose of 150 mg radiolabeled abemaciclib, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.[1]

SPECIFIC POPULATIONS

Age, Gender, and Body Weight

Based on a population pharmacokinetic (PopPK) analysis that included 134 males and 856 females with cancer, aged 24-91 years, and with body weight ranging from 36-175 kg, abemaciclib exposure was not affected by

- age
- gender, or
- body weight.[1-4]

Body weight changes may affect hepatic metabolism and elimination. However, no clinically significant effect of body weight on abemaciclib exposure was identified.[3,4]

A post hoc analysis from the monarchE trial evaluated the impact of baseline body mass index (BMI) on the efficacy and safety of adjuvant abemaciclib plus endocrine therapy (ET).[5]

Consistent invasive disease-free survival and distant relapse-free survival improvement at 5 years across all BMI subgroups was observed. Patients with Class 2 and 3 obesities had a 17% higher risk of disease recurrence compared with the nonoverweight subgroup.[5]

Safety outcomes were generally consistent across BMI subgroups, with a slightly higher incidence of serious adverse events in both treatment arms among patients with obesity, potentially influenced by older age and a greater number of comorbidities.[5]

Renal Impairment

In a PopPK analysis, mild and moderate renal impairment had no effect on the exposure of abemaciclib.[1]

The PopPK analysis evaluated 990 individuals including

- 381 individuals with mild renal impairment (60 mL/min ≤ creatinine clearance [CrCL] <90 mL/min), and
- 126 individuals with moderate renal impairment (30 mL/min ≤ CrCL <60 mL/min).[1]

Dose adjustment is not required in patients with mild or moderate renal impairment (CrCL ≥30-89 mL/min, estimated by Cockcroft-Gault [CG]).[1]

The PK of abemaciclib is unknown in patients

- with severe renal impairment (CrCL <30 mL/min, CG)
- with end stage renal disease, or
- on dialysis.[1]

Hepatic Impairment

Relative to subjects with normal hepatic function (n=10), following a single 200 mg oral dose of abemaciclib, the relative potency adjusted unbound area under the curve from time zero to infinity ($AUC_{0\text{-}INF}$) of abemaciclib plus its active metabolites (M2, M18, M20) in plasma increased

- 1.2-fold in subjects with mild hepatic impairment (Child-Pugh A, n=9)
- 1.1-fold in subjects with moderate hepatic impairment (Child-Pugh B, n=10), and
- 2.4-fold in subjects with severe hepatic impairment (Child-Pugh C, n=6).[1]

In subjects with severe hepatic impairment, the abemaciclib $t_{1/2}$ increased to 55 hours compared to 24 hours in subjects with normal hepatic function.[1]

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B).[1]

For patients with severe hepatic impairment (Child-Pugh C), reduce the abemaciclib dosing frequency to once daily.[1]

CARDIAC ELECTROPHYSIOLOGY

Based on evaluation of the corrected QT (QTc) interval in patients and in a healthy volunteer study, abemaciclib did not cause large mean increases (ie, 20 ms) in the QTc interval.[1,6]

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ENCLOSED PRESCRIBING INFORMATION

VERZENIO® (abemaciclib) tablets, for oral use, Lilly

REFERENCES

The published references below are available by contacting 1-800-LillyRx (1-800-545-5979).

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