EDURANT® (rilpivirine)
EDURANT - Pharmacokinetic Food Effects

SUMMARY

- Administration of EDURANT without food or with a nutritional drink reduced the exposure by approximately 40-50% compared with administration with a standard meal.[1]

PHARMACOKINETIC STUDY

Crauwels et al (2013)[1] evaluated the effect of fasting conditions and different meal types on rilpivirine (RPV) exposure.

Study Design/Methods

- This was a phase 1, open-label, randomized, 4-way crossover study in HIV-negative healthy subjects (N=20; 90% male; median age, 34.5 years).
- All subjects were administered 1 single EDURANT 75 mg tablet (75 mg formulation compositionally proportional to commercial 25 mg tablet) in 4 different sessions (random order), each separated by a washout period of ≥13 days. Subjects fasted for 10 hours, overnight, prior to each EDURANT administration.
  - Normal-fat breakfast (533 kcal): standard breakfast (4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired)
  - Fasting conditions (0 kcal): fasted ≥10 hours prior to dosing, until 4 hours after dosing
  - High-fat breakfast (928 kcal): high-fat breakfast (2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with one slice of cheese and 240 mL of whole milk)
  - Protein-rich drink (300 kcal): nutritional drink (240 mL of Ensure® HP)
- Pharmacokinetic (PK) parameters for RPV including peak concentrations (C_{max}), time to C_{max} (t_{max}), half-life ($t_{1/2}$), area under the plasma concentration-time curve (AUC), safety, and tolerability were evaluated.

Pharmacokinetic Results

- PK parameters for RPV administered after each treatment session are provided in Table: RPV PK Parameters.
  - The mean plasma concentration-time profiles for RPV, when administered with a normal-fat and high-fat breakfast, were comparable.
  - When EDURANT was administered in a fasted state, RPV AUC_{last} and C_{max} were reduced by 43% and 46%, respectively compared with a normal-fat breakfast. Likewise, when administered with a protein-rich drink, RPV AUC_{last} and C_{max} were reduced by 50% each.

RPV PK Parameters[1]

Parameter	Normal-Fat Breakfast (Ref: n=19)	Fasting Conditions (Test: n=19)	High-Fat Breakfast (Test: n=19)	Protein-Rich Drink (Test: n=18)
Mean C_{max}, ng/mL (SD)	296±118	170±66	280±103	156 ± 60
Median t_{max}, hrs (range)	5 (2-9)	4 (2-24)	5 (3-9)	5 (4-9)
Mean AUC_{last}, ng•h/mL (SD)	10,340±3894	6320±2339	9717±3535	5437±2421
Mean AUC_{inf}, ng•h/mL (SD)	11,450±4431	7202 ± 3024	10,670±4331	6094±3047
Mean $t_{1/2,term}$, hrs[a] (SD)	48±22	55±28	43±17	47±23
Least-squares means ratio for test to reference (90% confidence interval)				
C_{max}	-	0.54 (0.43-0.69)	0.92 (0.81-1.05)	0.50 (0.40-0.63)

AUC_{last}	-	0.57 (0.46-0.72)	0.92 (0.80-1.07)	0.50 (0.41-0.61)
AUC_{inf}	-	0.59 (0.47-0.74)	0.91 (0.79-1.05)	0.51 (0.42-0.62)

Abbreviations: AUC_{inf}, area under the plasma concentration time curve from time point zero to infinity; AUC_{last}, area under the plasma concentration time curve from administration until the last timepoint with a measurable concentration; C_{max}, maximum plasma concentration; PK, pharmacokinetic; Ref, reference; SD, standard deviation; $t_{1/2,term}$, terminal elimination half-life; t_{max}, time to C_{max}.
[a]Accurate determination of $t_{1/2, term}$ was not possible in all volunteers because $t_{1/2, term}$ was relatively long compared to the sampling of up to 168 hours (applicable to 5 volunteers when EDURANT was administered with a normal-fat breakfast, 9 volunteers when administered under fasting conditions, 3 volunteers when administered with a high-fat breakfast, and 6 volunteers when administered with a protein-rich drink).

Safety

- Five subjects reported 5 separate treatment-emergent adverse events (AEs) all rated DAIDS grade 1 or 2 (mild or moderate) in intensity [DAIDS: Division of Acquired Immunodeficiency Syndrome (grades the severity of adult and pediatric AEs)].
- One case of hot flush, reported when EDURANT was administered with a normal-fat breakfast, was considered possibly related to EDURANT.
- No AEs led to treatment discontinuation.
- Treatment-emergent laboratory abnormalities, primarily grade 1 or 2, were reported in all subjects.
    - One grade 4 transient hyponatremia occurred when EDURANT was administered with a high-fat breakfast.
    - Fifteen grade 3 abnormalities were reported in 8 subjects.
    - An overestimation of these graded laboratory abnormalities may have occurred because local laboratory normal ranges did not always correspond to the DAIDS graded abnormalities defined in the protocol.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 08 September 2023.

REFERENCES

1. Crauwels HM, Heeswijk RPG van, Buelens A, et al. Impact of food and different meal types on the pharmacokinetics of rilpivirine. *J Clin Pharmacol*. 2013;53(8):834-840.