INTELENCE® (etravirine)
INTELENCE - Tablet Dispersion

SUMMARY

- Instruct patients to swallow the INTELENCE tablet(s) whole with liquid such as water. Patients who are unable to swallow the INTELENCE tablet(s) whole may disperse the tablet(s) in water. Instruct the patient to do the following[1]:
  - Place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough liquid to cover the medication,
  - Stir well until the water looks milky,
  - Add approximately 15 mL (1 tablespoon) of liquid. Water may be used but other liquids, such as orange juice or milk, may improve taste. Patients should not place the tablets in orange juice or milk without first adding water. The use of warm (temperature greater than 104°F [greater than 40°C]) or carbonated beverages should be avoided.
  - Drink the mixture immediately,
  - Rinse the glass several times with orange juice, milk or water and completely swallow the rinse each time to make sure the patient takes the entire dose.
- Study TMC125-C173 evaluated the relative single dose oral bioavailability of an etravirine (ETR) 100 mg tablet (phase 3 formulation) dispersed in water in human immunodeficiency virus (HIV)-1-negative, healthy subjects (N=37).[2]
  - No significant changes in pharmacokinetic (PK) values (maximum plasma concentration [C_{max}], area under the plasma concentration-time curve from time of administration up to the last time point with a measurable concentration postdosing [AUC_{last}], and area under the plasma concentration-time curve to infinity [AUC_{∞}]) were observed in subjects who received the dispersed tablet.
- The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1090 study evaluated the PK, safety, and efficacy of INTELENCE tablets in treatment-experienced HIV-infected patients aged 1 to <6 years (N=26).[3]
  - The geometric mean (GM) ETR area under the plasma concentration-time curve from time of administration to 12 h after dosing (AUC_{12h}) was 3.8-fold higher in patients who swallowed whole tablet vs those who took dispersed tablet (n=4 vs n=16; 10,721 vs 2841 ng·h/mL; *P*<0.0001).

PHARMACOKINETICS

Pharmacokinetic Study

Kakuda et al (2013)[2] conducted a phase 1, open-label, three period, crossover study that evaluated the relative single dose oral bioavailability of an ETR 100 mg tablet (phase 3 formulation) dispersed in water in HIV-1-negative, healthy subjects (N=37).

Study Design/Methods

- All subjects were scheduled to complete each of the following treatment sessions separated by washout periods of ≥14 days:
  - ETR 100 mg tablet swallowed whole
  - ETR 100 mg tablet dispersed in 100 mL water
  - ETR 100 mg (four 25 mg tablets) swallowed whole
- All ETR doses were administered with approximately 200 mL of water between 08:00 and 10:00.
  - The ETR dispersion was well stirred and ingested immediately. The glass was rinsed with water several times and each rinse was completely swallowed to ensure consumption of the entire dose.
  - Water intake was not permitted 2 hours before and 2 hours after ETR administration.
  - A standardized breakfast and lunch were provided before and after ETR administration.

- PK analyses were conducted up to 96 hours postdose for each treatment.

Pharmacokinetics

- No significant change in PK values (C_{max}, AUC_{last}, and AUC_{∞}) were observed in subjects that received the dispersed ETR tablet. Please see Table: ETR PK Parameters.
- Irrespective of formulation, maximum ETR plasma concentrations were reached 4.5 hours postdose.
- Inter-subject variability (% coefficient of variation for C_{max}, AUC_{last} and AUC_{∞}) was comparable between treatment with ETR 100 mg and 25 mg noncoated tablets and higher with the 100 mg dispersion (47%-79%).

ETR PK Parameters[2]

Parameters	ETR 100 mg tablet (N=37)		ETR 100 mg tablet (dispersed in 100 mL water) (N=33)		ETR 100 mg (four 25 mg tablets) (N=35)	
	Mean± SD	GM (% CV)	Mean±SD	GM (% CV)	Mean±SD	Geometric Mean (% CV)
C_{max}, ng/mL	130±50	120.9 (38.49)	131±62	117.3 (47.20)	113±44	103.6 (38.96)
AUC_{last}, ng·h/mL	1241±642	1098 (51.68)	1219±712	1064 (58.45)	1126±542	996.6 (48.14)
AUC_{∞}, ng·h/mL	1412±885	1221 (32.67)	1409±1109[a]	1182 (78.69)	1286±751	1116 (58.43)

Abbreviations: AUC_{last}, area under the plasma concentration-time curve from time of administration up to the last time point with a measurable concentration postdosing; AUC_{∞}, area under the plasma concentration-time curve to infinity; CV, coefficient of variation; C_{max}, maximum plasma concentration; ETR, etravirine; GM, geometric mean; PK, pharmacokinetic; SD, standard deviation.
[a]Accurate determination not possible.

- ETR C_{max} and AUC_{last} (LSM ratios) for the 100 mg dispersion were comparable to the ETR 100 mg noncoated tablet swallowed whole with 90% CIs in the 80-125% "no effect" range.

Least Square Means Ratios for ETR Tablet Formulations[2]

LSM ratios, % (90% CI)	ETR 100 mg (four 25 mg tablets) vs ETR 100 mg tablet swallowed whole	ETR 100 mg tablet (dispersed in 100 mL water) vs ETR 100 mg tablet swallowed whole
C_{max}, ng/mL	85.4 (78.08-93.4)	95.33 (87.78-103.5)
AUC_{last}, ng·h/mL	91.18 (84.88-97.95)	96.54 (90.48-103.0)
AUC_{∞}	91.73 (84.93-99.06)	–

Abbreviations: AUC_{last}, area under the plasma concentration-time curve from time of administration up to the last time point with a measurable concentration postdosing; AUC_{∞} area under the plasma concentration-time curve to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; ETR, etravirine; LSM, least square means.

Safety

- All adverse events (AEs) were grade 1 or 2 in severity, except for one grade 3 AE (asymptomatic increase in lipase, with no increase in amylase, which resolved spontaneously following study withdrawal).
- No serious AEs or deaths were reported.
- The incidence of AEs was comparable between the dispersed ETR tablet and whole tablet regimens; the most commonly reported AE considered possibly related to treatment was headache (8%).
- No AEs related to the taste, odor, or texture of the dispersed medication were received.

Pharmacokinetics, Safety, and Efficacy Study in Pediatric Patients (IMPAACT P1090)

MacBrayne et al (2021)[3] conducted a phase I/II, multicenter, open-label study (IMPACT P1090) that evaluated the PK, safety, and efficacy of INTELENCE in treatment-experience HIV-infected patients aged 1 to <6 years (N=26).

Study Design/Methods

- Treatment-experience patients aged ≥1 to <6 years with plasma HIV-1 RNA levels above 1000 copies/mL were enrolled into 2 age cohorts (cohort 1, ≥2 to <6 years; cohort 2, ≥1 to <2 years).
- All patients received INTELENCE tablets (swallowed whole or dispersed in liquid) in combination with an optimized background regimen (OBR) containing a ritonavir-boosted protease inhibitor (PI/r).
- Patients received their dose of INTELENCE tablet within 30 minutes of consuming an age-appropriate (nonstandardized) meal.
- All patients underwent 12 hours of intensive PK sampling 7-18 days after initiating INTELENCE tablets.
- During the intensive PK visit, to quantify ETR in plasma, whole blood was collected predose and at 1, 2, 4, 6, 9, and 12 hours postdose.
- PK dose adjustment was performed for patients who did not achieve the target AUC_{12h} (2864 ng·h/mL).
- In each cohort, PK and safety were evaluated through week 4 in the first 6 patients (mini cohort) before enrolling additional patients. The target GM ETR AUC_{12h} for this mini cohort was 2713-6783 ng·h/mL.
- In cohort 1, 6 patients received INTELENCE tablets at a dose of 5.2 mg/kg twice daily (BID). The exposures with this dose failed to meet the protocol-defined PK criteria; thus, the dose was revised based on weight as follows:
    - 8 to <10 kg: 75 mg BID
    - 10 to <20 kg: 100 mg BID
    - 20 to <25 kg: 125 mg BID

Pharmacokinetics

- Of the 26 patients enrolled in the study, 25 (96.2%) were included in the intensive PK analysis.
- Of the first 6 patients in cohort 1 (mini cohort) who received a weight-based dose (5.2 mg/kg BID), 4 (66.7%) received a dose of 75 mg BID and 2 (33.3%) received a dose of 100 mg BID. Half of the patients took dispersed ETR.
    - A total of 2 patients (1 took the tablets dispersed and the other swallowed) required a dose increase due to AUC_{12h} <2350 ng·h/mL.
    - The exposures with this weight-based dose (AUC_{12h}, 2576 ng·h/mL) were below the protocol-defined criteria, and a revised dosing strategy was used for patients who were subsequently enrolled.

- Both cohorts passed the protocol-defined PK and safety criteria after using the revised weight-based dosing strategy. Please see Table: PK Parameters of ETR in Patients Who Received the Final Weight-Based Dose.

PK Parameters of ETR in Patients Who Received the Final Weight-Based Dose[3]

	GM (% CV)	Mean (SD)	Median (Range)
Cohort 1 (n=15)			
AUC_{12h} (ng·h/mL)	3823.1 (75.1)	4813.6 (3614.0)	3709.4 (1220.5-12,998.6)
C_{max} (ng/mL)	465.8 (69.0)	564.6 (389.4)	457.8 (199.1-1494.0)
C_{last} (ng/mL)	232.4 (87.8)	328.2 (288.3)	253.0 (54.3-962.0)
T_{max} (h)	4.5 (40.3)	4.8 (1.9)	4.0 (2.0-9.0)
CL/F (L/h/m^2)	39.8 (62.2)	48.9 (30.4)	41.7 (10.6-117.8)
Individual ETR dose increase required (AUC_{12h} <2350 ng·h/mL)	5 (33.0)	NA	NA
Cohort 2 (n=6)			
AUC_{12h} (ng·h/mL)	3328.1 (75.5)	4158.6 (3137.8)	3389.7 (1148.1-9989.8)
C_{max} (ng/mL)	390.4 (71.3)	489.9 (349.4)	379.3 (121.9-1085.0)
C_{last} (ng/mL)	225.5 (80.0)	278.3 (222.6)	186.5 (101.9-706.0)
T_{max} (h)	2.0 (65.7)	2.5 (1.6)	2.5 (1.0-4.0)
CL/F (L/h/m^2)	54.3 (72.7)	67.1 (48.8)	54.6 (18.4-156.8)
Individual ETR dose increase required (AUC_{12h} <2350 ng·h/mL)	2 (33.0)	NA	NA

Abbreviations: AUC_{12h}, area under the plasma concentration-time curve from time of administration to 12 h after dosing; CL/F, apparent oral clearance; C_{last}, last measurable concentration in the dosing interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; ETR, etravirine; GM, geometric mean; NA, not applicable; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum plasma concentration.

- In cohort 1 (n=15), 11 (73.3%) patients received dispersed ETR (1 patient dispersed the 100 mg tablet and swallowed the 25 mg tablet) and 3 swallowed the tablet(s) whole.
- In cohort 2 (n=6), 5 (83.3%) patients received dispersed ETR.
- Overall, 7 (33.3%) patients who received dispersed ETR had an AUC_{12h} <2350 ng·h/mL and required an ETR dose increase.
- Median age and weight, respectively, were 3.8 years and 14.3 kg among those taking dispersed tablet and 5.7 years and 16.3 kg among those taking whole tablet.
- The GM ETR AUC_{12h} was 3.8-fold higher in patients who swallowed whole tablet vs those who took dispersed tablet (n=4 vs n=16; 10,721 vs 2841 ng·h/mL; *P*<0.0001).
- Median ETR AUC_{12h} was comparable between dispersed ETR in water vs dispersed ETR in another liquid (2975 ng·h/mL vs 3128 ng·h/mL).

Palatability and Adherence

- No issues were reported by the patients or their caregivers in taking INTELENCE tablet at 58 (89%) of the 65 palatability assessments.
- For 4 patients, challenges while taking INTELENCE tablet were reported (1 in cohort 1 and 3 in cohort 2); 2 refused most doses and 2 infrequently refused doses. Of these 4 patients, 3 were taking dispersed INTELENCE and 1 was taking a combination of swallowed and dispersed tablet.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 13 February 2025.

REFERENCES

1. INTELENCE (etravirine) [Prescribing Information]. Titusville, NJ: Janssen Therapeutics, Division of Janssen Products, L.P; https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INTELENCE-pi.pdf.

2. Kakuda TN, Berckmans C, De Smedt G, et al. Single-dose pharmacokinetics of pediatric and adult formulations of etravirine and swallowability of the 200-mg tablet: results from three phase 1 studies. *Int J Clin Pharmacol Ther*. 2013;51(9):725-737.

3. MacBrayne CE, Rutstein RM, Wiznia AA, et al. Etravirine in treatment-experienced HIV-1-infected children 1 year to less than 6 years of age. *AIDS*. 2021;35(9):1413-1421.