Splitting or Crushing *Triumeq* Tablets

Summary

- An open-label, 3-period, randomized, pharmacokinetic (PK) study was conducted evaluating the bioequivalence of *Triumeq* (abacavir/dolutegravir/lamivudine, ABC/DTG/3TC) when crushed in fasted and fed (enteral nutrition) states compared to whole tablet in the fasted state. Bioequivalence could not be demonstrated as the 90% confidence interval (CI) of the geometric mean ratio (GMR) fell outside the pre-defined bioequivalence range for some of the PK parameters for DTG and ABC.[1] The increase in DTG exposure and decrease in ABC Cmax were not considered clinically relevant. No serious adverse events (SAE) were reported.
- The efficacy and safety of splitting ABC/DTG/3TC tablets prior to administration has not been studied. ABC/DTG/3TC is a film-coated, non-scored, and non-sustained released tablet formulation. Based on the physiochemical and pharmacokinetic characteristics, splitting ABC/DTG/3TC tablets is not expected to affect the absorption of the active ingredients.
- To ensure administration of the entire dose of ABC/DTG/3TC, the tablet(s) should be ideally swallowed whole. For patients who have difficulty swallowing, splitting or crushing ABC/DTG/3TC tablets may be an acceptable alternative. In these patients, ABC/DTG/3TC tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.
- Important safety information is found in the attached Prescribing Information.
- The prescribing information for this product contains a boxed warning. Please consult the WARNING section of the attached prescribing information for further details and for important safety information.

PHARMACOKINETICS OF ABC/DTG/3TC WHEN CRUSHED

An open-label, 3-period, randomized, single dose, cross-over, PK study was conducted in 22 healthy, HIV-negative subjects evaluating the bioequivalence of abacavir/dolutegravir/lamivudine when crushed.[1] Subjects received the following randomized treatments with a 7-day wash-out period between treatments:

- reference treatment (whole tablet in fasted state)
- intervention I (crushed and suspended in fasted state)
- intervention II (crushed and suspended with 250 mL Nutrison® enteral nutrition taken orally)

Forty-eight-hour PK parameters were measured for all medications in the ABC/DTG/3TC single tablet regimen (STR). Bioequivalence could be accepted when the 90% CI of the GMR fell within the 80% to 125% (0.80 - 1.25) pre-defined bioequivalence range.

Table 1. Pharmacokinetics of ABC/DTG/3TC with and without Enteral Nutrition[1]

ABC/DTG/3TC Components	PK Parameter	Reference treatment, (Whole Tablet, Fasting) Geometric Mean (%CV)	Intervention I, (Crushed Tablet, Fasting) Geometric Mean (%CV)	Intervention II (Crushed Tablet, Enteral Nutrition) Geometric Mean (%CV)
DTG 50 mg	AUC $_{0-\infty}$ (mg/L*h)	69.50 (22)	87.49 (15)	82.38 (15)
	C $_{max}$ (mg/L)	3.81 (24)	4.94 (18)	4.65 (15)
	T_{max} (h)	2.27 (1.00-4.02)	2.00 (0.50-3.00)	2.50 (1.50-4.02)
	T ½ (h)	13.65 (13)	13.63 (20)	13.24 (14)
ABC 600 mg	AUC $_{0-\infty}$ (mg/L*h)	14.40 (30)	14.31 (30)	13.55 (25)
	C $_{max}$ (mg/L)	4.88 (30)	4.95 (31)	4.06 (22)
	T_{max} (h)	1.00 (0.50-2.50)	1.00 (0.50-2.00)	1.58 (0.50-2.50)
	T ½ (h)	3.87 (21)	4.33 (26)	4.05 (22)
3TC 300 mg	AUC $_{0-\infty}$ (mg/L*h)	14.20 (26)	14.23 (21)	14.30 (21)
	C $_{max}$ (mg/L)	2.31 (31)	2.28 (23)	2.47 (21)
	T_{max} (h)	2.00 (1.00-3.00)	1.50 (1.00-4.00)	2.00 (1.50-3.00)
	T ½ (h)	13.88 (35)	13.15 (32)	12.27 (27)

%CV = coefficient of variance; 3TC = lamivudine; ABC = abacavir; AUC $_{0-\infty}$ = area under the concentration-time curve extrapolated to infinity; C $_{max}$ = maximum plasma concentration; CI= confidence interval; T ½ = half-life, apparent, median; T_{max} = time to maximum plasma concentration, median (range).

ABC/DTG/3TC Components	PK Parameter	GMR (90% CI) Intervention I vs. Reference	GMR (90% CI) Intervention II vs. Reference
DTG 50 mg	AUC $_{0-\infty}$ (mg/L*h)	1.26 (1.19-1.33)	1.18 (1.12-1.25)
	C $_{max}$ (mg/L)	1.30 (1.23-1.36)	1.22 (1.15-1.28)
ABC 600 mg	AUC $_{0-\infty}$ (mg/L*h)	0.99 (0.95-1.04)	0.94 (0.90-0.98)
	C $_{max}$ (mg/L)	1.01 (0.93-1.10)	0.83 (0.76-0.90)
3TC 300 mg	AUC $_{0-\infty}$ (mg/L*h)	1.00 (0.96-1.05)	1.01 (0.96-1.05)
	C $_{max}$ (mg/L)	0.99 (0.93-1.05)	1.07 (1.00-1.13)

GMR = geometric mean ratio, 3TC = lamivudine; ABC = abacavir; AUC $_{0-\infty}$ = area under the concentration-time curve extrapolated to infinity; C $_{max}$ =maximum plasma concentration; CI= confidence interval.

Table 2. ABC/DTG/3TC Bioequivalence when Crushed[1]

The criteria for bioequivalence were not met as the 90% CI of the GMR summarized in Table 2 fell outside the pre-defined bioequivalence range for DTG (AUC $_{0-\infty}$, C_{max}) and ABC (C_{max}). However, the increase in exposure to the DTG component (Interval I vs. Reference: AUC $_{0-\infty}$, C $_{max}$ and Interval II vs. Reference: C_{max}) of ABC/DTG/3TC was not considered clinically relevant since DTG exposure when taken with food or when given twice daily exceeds the results provided in Table 1. The decreased ABC C_{max} (Intervention II vs. Reference) was in line with other studies for ABC taken with food.

No SAEs were reported during the trial. One or more adverse events were reported in 77% of subjects. The most common AEs of any type reported were headache (27%), nausea (18%), fatigue (18%), and dizziness, abdominal pain and diarrhea (all 14%); there were no differences in number or type of AE reported in the intervention periods compared to the reference period.

The study did not evaluate the PK of DTG 50 mg twice daily when crushed with or without enteral nutrition.

SPLITTING ABC/DTG/3TC

The efficacy or safety of splitting ABC/DTG/3TC tablets prior to administration has not been studied. ABC/DTG/3TC is a film-coated, non-scored, and non-sustained released tablet formulation.[2] Administration of split tablets is not expected to alter the clinical effect. This conclusion is based on the physiochemical and pharmacokinetic characteristics of the active ingredients and the *in vitro* dissolution behavior of ABC/DTG/3TC tablets in water, assuming the patients splits and transfers 100% of the tablet and ingests immediately.

OTHER DATA

To ensure administration of the entire dose of ABC/DTG/3TC, the tablet(s) should be ideally swallowed whole without splitting or crushing.[2] For patients who have difficulty swallowing, splitting or crushing ABC/DTG/3TC tablets may be an acceptable alternative. In these patients, ABC/DTG/3TC tablets may be split or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately. Administration of split tablets, or crushed tablets with a small amount of semi-solid food or liquid is not expected to have an adverse impact on the pharmaceutical quality, and would therefore not be expected to alter the clinical effect.

Some information contained in this response may not be included in the approved Prescribing Information for this product. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877–844–8872. Please consult the attached Prescribing Information.

This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCES

1. Roskam-Kwint M, Bollen P, Colbers A, Duisenberg-van Essenberg M, Harbers V, Burger D. Crushing of dolutegravir fixed-dose combination tablets increases dolutegravir exposure. *J Antimicrob Chemother.* 2018;73(9):2430-2434. doi:http://dx.doi.org/10.1093/jac/dky191.
2. Data on File. DNG2014N201372_00.