OFFICE OF CLINICAL PHARMACOLOGY (OCP) ADDENDUM

NDA	211284 (EDR Link)
Date of Submission	Jan 16, 2018
Generic Names	Lamivudine (3TC) and Tenofovir Disoproxil Fumarate (TDF)
Clinical Pharmacology Review Team	Vikram Arya, Ph.D., FCP, Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Celltrion, INC
Application Type	505 (b) (2)
Formulation; strength(s) to-be-marketed	Fixed Dose Combination (FDC) Tablets; 300 mg 3TC/300 mg TDF

Background

Celltrion INC (applicant) is seeking approval of Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF) 300 mg/300 mg FDC tablets based on the results of trial CT-G02 1.2, a single dose relative bioavailability trial conducted under *fasting conditions* and CT-G02 1.1, a single dose relative bioavailability trial conducted under *fed conditions*. The clinical pharmacology review of both relative bioavailability trials was checked into DARRTS on 09/13/2018.

The applicant did not provide adequate storage stability data to cover the entire duration of sample storage. For both trials, 44 days of storage stability data at ~-70 °C was provided whereas the samples were stored for 134 days (for samples collected in trial CT-G02 1.2) and for 129 days (for samples collected in trial CT-G02 1.1). The Office of Clinical Pharmacology (OCP) reviewed the information provided in the NDA and concluded that the information supports the approval of the application **pending acceptability of the additional storage stability data**. The applicant was requested (on 09/14/2018) to provide additional storage stability data to cover the entire duration of sample storage.

This addendum includes an assessment of the additional stability data provided by the applicant on 09/17/2018.

Additional Sample Storage Stability Data (EDR Link)

Quality control samples at high and low concentrations of tenofovir and lamivudine were prepared on 29 September 2017 and stored frozen at ~ -70ºC in human K_2EDTA plasma in polypropylene tubes until used. On 07 March 2018, the samples were thawed in a water bath at 22ºC and assayed with a set of freshly prepared calibration standards and quality control samples.

The table below compares the concentrations of tenofovir and lamivudine in the stored samples with the freshly prepared QC samples at two different concentrations.

Table 1: Comparison of the tenofovir and lamivudine in the stored samples with the freshly prepared QC samples at two different concentrations

Replicates	Tenofovir		Lamivudine	
	High Concentration (450 ng/ml)	Low Concentration (14.0 ng/ml)	High Concentration (3750 ng/ml)	Low Concentration (117.0 ng/ml)
1	458	14.2	3669	117.5
2	467	14.4	3905	120.4
3	454	14.5	3644	121.9
4	470	14.8	3632	120.9
5	456	15.5	3742	122.1
6	471	13.8	3836	122.1
Mean	463	14.5	3738	120.8
% CV	1.6	4.0	3.0	1.5
% Bias	2.9	3.6	-0.3	3.2
N	6	6	6	6

Source: Method Validation Report-Addendum 1, Page 18

Conclusion

The applicant has demonstrated adequate long-term storage stability of tenofovir and lamivudine at ~-70°C in human K_2EDTA plasma for 159 days. The information provided by the applicant addresses the clinical pharmacology comment regarding lack of long term sample storage stability data in the original review and there are no remaining clinical pharmacology issues that would preclude approval of the application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIKRAM ARYA
10/21/2018

KELLIE S REYNOLDS
10/22/2018