

## 1.0 Abstract

### Title

Drug Use Investigation of Kaletra tablets (QD) in patients with HIV-infection

### Keywords

Kaletra, lopinavir (LPV)/ritonavir (RTV), Post Marketing Observational Study (PMOS), quaque die (QD), Human Immunodeficiency Virus (HIV) infection

### Rationale and Background

Kaletra is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 protease. As co-formulated in Kaletra, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

HIV infection is considered to be a chronic disease requiring lifelong therapy. Therefore, there is a need for products that have not only persisting effects but also higher level of convenience, thereby improving the drug intake rate.

Clinical studies (M99-056, M05-730<sup>1</sup>, M06-802<sup>2</sup>, and M02-418<sup>3</sup>) showed no critical differences in the efficacy and safety between QD administration and *bis in die* (BID) administration of LPV/RTV.

In clinical studies, there was no clinically significant difference in frequency of adverse events observed between BID administration and QD administration of LPV/RTV. As such, information on QD administration of LPV/RTV was included in the ongoing post-marketing survey of Kaletra tablets (Protocol: [REDACTED] after approval was obtained from the PMDA for QD dosing.

### Research Question and Objectives

The Drug Use Investigation of Kaletra tablets (generic name: lopinavir/ritonavir) was conducted to clarify the following with regard to treatment with Kaletra tablets:

- 1) Incidence of adverse drug reactions in the clinical setting

2) Factors that may affect the safety and effectiveness of Kaletra QD treatment.

The present survey was conducted as a part of the Collaborative Drug Use Investigation of HIV-Related Drugs (HRD Cooperative Survey) that was performed according to the following notifications:

- Notification on the collaborative Drug Use Investigation during the reexamination periods for HIV-related drugs (Notification No. 38 of the Research and Development Division, PAB dated June 26, 1997)
- Notification on handling the postmarketing surveillance of HIV-related drugs (Notification No.1746 of the Evaluation and Licensing Division, PMSB dated December 13, 1999)
- Notification on modification of handling the postmarketing surveillance of HIV-related drugs (Notification No. 1007001 of the Evaluation and Licensing Division, PFSB dated October 7, 2005)

For the detail of organization of HRD Cooperative Survey, please see [REDACTED]

### **Study Design**

The investigation was performed as a single cohort, non-interventional observational study, as instructed by the regulatory authorities, for the purpose of evaluating the safety and effectiveness of Kaletra tablets in patients with HIV infection under actual clinical practice.

As of the time of approval of this additional dosage regimen, information on QD administration was also collected in the post-marketing survey of Kaletra tablets (Protocol: [REDACTED]) ongoing in the HRD Cooperative Survey.

### **Setting**

This PMOS was conducted during the 15th year of the HRD Cooperative Survey.

- Registration period: From April 2011 to March 2012
- CRF retrieval period: From April 2012 to March 2013

## **Subjects and Study Size, Including Dropouts**

### <Subjects>

Patients who were receiving Kaletra or who started Kaletra therapy during the registration period were evaluated.

Indication: HIV infection

Dosage regimen: Usually, adult patients should be treated with lopinavir/ritonavir at a dose of 400/100 mg BID (2 tablets twice daily) or 800/200 mg QD (4 tablets once daily). Children weighing 40 kg may receive lopinavir/ritonavir at a dose of 400/100 mg BID (2 tablets twice daily). Kaletra tablets may be taken with or without food.

### <Study Size>

As much as possible, all patients who received Kaletra for the treatment of HIV infection in institutions participating in the HRD Cooperative Survey during the registration period were evaluated.

However, the maximum number of patients to be evaluated was specified for each institution treating a large number of patients in order to maintain the quality of the survey.

Over the enrollment period (April 2011 to March 2012), 236 patients were included for evaluation. 16 patients completed treatment with Kaletra tablets prior to April 2011, as such 220 patients were included in the safety analysis set and the effectiveness analysis set of this report.

## **Variables and Data Sources**

Please see the information shown in 

## **Results**

The survey was conducted as the 15th annual survey in the HRD Cooperative Survey. 236 patients were enrolled from 23 centers between April 1, 2011 and March 31, 2012, and

survey forms for all patients were collected and all data queries were resolved by March 31, 2013. Of patients from whom survey forms were collected, 16 patients completed treatment with Kaletra tablets before the start of enrollment (April 1, 2011), and as such, these patients were excluded from patients included in the safety analysis set. As a result, the number of patients included in the safety analysis set and the effectiveness set was 220.

The proportion of males was 93.18% (205/220), and the mean age was 43.6 years. The majority of patients were Japanese with a percentage of 92.73% (204/220). Proportions of patients with renal disorder and patients with liver disorder among concomitant diseases were 1.36% (3/220) and 27.73% (61/220), respectively. The proportion of patients with haemophilia was 7.73% (17/220).

The most common daily dose of Kaletra tablets was “BID” in 70.91% (156/220), followed by “4 tablets x 1 time per day” in 25.45% (56/220). 2 tablets x 2 times per day changing to 4 tablets x 1 time per day was 2.27 % (5/220), other was 0.91% (2/220) and unknown was 0.45% (1/220).

The mean use duration of Kaletra tablets was 372.6 days. Among anti-HIV drugs that were used concomitantly, “Nucleoside reverse transcriptase inhibitors” were most commonly used with a rate of 97.27% (214/220).

#### <Safety>

In the safety analysis set (220 patients), there were 83 patients with adverse drug reactions (frequency: 37.73%, 83/220), and there were 124 reports of adverse drug reactions. Adverse drug reactions (with frequency of 2% or higher) were hypertriglyceridaemia in 9.09% (20/220), hyperlipidaemia in 6.36% (14/220), blood triglycerides increased in 5.91% (13/220), diarrhoea in 4.09% (9/220), gamma-glutamyltransferase increased in 3.64% (8/220), and blood alkaline phosphatase increased in 2.73% (6/220).

The number of patients with serious adverse events was 4 patients (1.82%). All of the events which included osteonecrosis (2 patients) and anal cancer (1 patient) and cardiac failure (1 patient) were considered related to drug.

Treatment characteristics in patients receiving QD administration (56 patients) and patients receiving BID administration (158 patients) (note that 6 patients received another administration), and the frequency of adverse drug reactions was 30.36% (17/56) and 41.14% (65/158), respectively. In patients receiving BID administration, the frequencies of blood triglycerides increased, gamma-glutamyltransferase increased, and blood alkaline

phosphatase increased were 8.23% (13/158), 4.43% (7/158), and 3.80% (6/158), respectively. All of the events were known adverse drug reactions. In patients receiving QD administration, hypertriglyceridaemia occurred in 10.71% (6/56) and gamma-glutamyltransferase increased in 1.79% (1/56).

#### <Effectiveness>

Since there were differences in the effectiveness between treatment-experienced and treatment-naïve patients, the effectiveness data were summarized separately for these 2 groups. In treatment-naïve patients, the mean CD4 lymphocyte count (cells/mm<sup>3</sup>) at the start of treatment was 144.5 (6 patients). The count was 184.3 after 24 months of treatment and 330.0 after 36 months of treatment in treatment-naïve patients.

On the other hand, in patients with treatment experience, the mean CD4 lymphocyte count (cells/mm<sup>3</sup>) at the start of treatment was 654.5 (4 patients). The count was 713.5 after 9 months of treatment and 878.5 after 12 months of treatment in treatment-experienced patients.

However, this survey was a drug use investigation under the actual clinical practice, and as a result, the number of patients observed at both before and after the start of treatment with Kaletra tablets was extremely small. For this reason, CD4 lymphocyte counts were summarized also for patients observed at each time point after the start of treatment, regardless of presence/absence of observation before the start of treatment (0 months). As a result, the mean count was 211.0 (4 patients) for 24 months of treatment and 309.0 (3 patients) for 36 months of treatment in treatment-naïve patients, and was higher than 500 cells/mm<sup>3</sup> in all of the time points: 3, 6, 9, and 12 months in treatment-experienced patients.

In treatment-experienced and treatment-naïve patients, the mean plasma HIV-RNA amount (Log<sub>10</sub> copies/mL) at the start of treatment was 5.2 (6 patients) and 2.6 (4 patients), respectively, but it was 3.4 after 24 months of treatment and 2.6 after 36 months of treatment in treatment-naïve patients, and 2.6 each after 9 months and 12 months of treatment in treatment-experienced patients, showing viral suppression in both groups. Similarly to CD4 lymphocyte counts, the number of patients observed at both before and after the start of treatment was extremely small, and as such, amounts of plasma HIV-RNA were totalized also for patients observed at each time point after the start of treatment regardless of presence/absence of observation before the start of treatment (0 months). The mean plasma HIV-RNA amount was 2.6 to 3.2 in treatment-naïve patients

and 2.6 in treatment-experienced patients after the start of treatment at all of the time points: 3, 6, 9, and 12 months.

Regarding the effectiveness in treatment-experienced and treatment-naïve patients, there were many missing observation data, and the results were limited, but the absence of difference between treatment-naïve and treatment experienced patients was suggested.

### **Conclusion**

From the above results, in both the safety and effectiveness, no clinically relevant difference was demonstrated between QD administration and BID administration.

### **Marketing Authorisation Holder(s)**

AbbVie GK

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### **Names and Affiliations of Principal Investigators**

Not applicable