CASE STUDY 4 (*Continued*)

800–1000 cal with 150, 250, and 500–600 cal from protein, carbohydrate and fat, respectively), a low-fat, low-calorie meal (approximately 400–500 cal with 120, 250, and 28–35 cal from protein, carbohydrate and fat, respectively), or a moderate-fat, standard calorie meal (approximately 500–700 cal with 75–105, 250–350, and 175–245 cal from protein, carbohydrate, and fat, respectively). However, palbociclib absorption was very low in approximately 13% of the patient population under fasted condition. The reason for this observation is not clear since we cannot identify the study designed to understand the underlying mechanism in the public domain. It has been shown that food increased palbociclib exposure in this patient subgroup without altering that from the rest of other patients. Because food intake reduced the intersubject variability on palbociclib absorption, it is recommended that palbociclib be taken with food in the U.S. package insert of Ibrance (FDA, 2015).

EFFECTS OF GASTRIC ACID MODULATING AGENTS ON PHARMACOKINETICS OF INSOLUBLE DRUGS

Orally administered drugs with pH-dependent solubility, especially weak bases, may demonstrate altered drug absorption in patients with various gastric pH. Gastric pH can be affected by multiple factors, including physiological or pathological changes in patients (Haruma et al., 2000), acidic beverage (Malhotra et al., 2002), food (Lennard-Jones et al., 1968), and juice (Claytor et al., 1941). Gastric acid modulating agents are the other factor which significantly alters gastric pH. Three types of gastric acid modulating agents, including antacids, histamine H_2-antagonists (or H_2-blockers), and proton pump inhibitors (PPIs), are available. Antacids, such as calcium carbonate, magnesium hydroxide, and aluminum hydroxide, neutralize gastric acid resulting in a rapid increase in gastric pH with a relatively short duration. H_2-blockers, like famotidine and ranitidine, target histamine H_2 receptors in the gastric parietal cells and yield a reduced gastric acid secretion (FDA, 2014) with duration of approximately 12 h. Omeprazole and rabeprazole are examples of PPIs, which suppress gastric acid secretion by inhibition of the hydrogen/potassium adenosine triphosphatase system in the gastric parietal cell (FDA, 1989) for more than 24 h postdose. As anticipated, the exposure of drugs with pH-dependent solubility can be significantly different when a gastric acid modulating agent is given concomitantly. Hence it is suggested to assess this drug–drug interaction effect in the drug development to instruct safe and effective use of these drug products (Zhang et al., 2014).

CASE STUDY 5

Dasatinib is a kinase inhibitor that has been approved for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic, accelerated, myeloid or lymphoid blast phase, and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) since 2006 (FDA, 2006). It has been marked in the U.S. under the trade name of SPRYCEL®. The recommended starting dosages are 100 mg administered once daily for chronic phase CML, and 140 mg administered once daily for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL, respectively.

Dasatinib is insoluble in water and slightly soluble in ethanol and methanol. As a weak base, dasatinib (pK_a = 3.1, 6.8, 10.8) demonstrates pH-dependent solubility change, with significantly reduced solubility as pH increasing from 1 to 6.5. Tsume et al. (2015) reported that

(*Continued*)