Evaluation of Crushed Tablet for Oral Administration and the Effect of Food on Apixaban Pharmacokinetics in Healthy Adults

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ABSTRACT

Purpose: These studies evaluate the relative bioavailability of crushed apixaban tablets and the effect of food on apixaban pharmacokinetic properties.

Methods: An open-label, randomized, crossover study in 33 healthy adults compared the bioavailability of 2 × 5-mg apixaban tablets administered whole (reference), crushed and suspended in 30 mL of water, and crushed and mixed with 30 g of applesauce. A second open-label, randomized, crossover study in 22 healthy adults compared apixaban 1 × 5-mg tablet administered when fasted (reference) or immediately after consumption of a high-fat, high-calorie meal. Point estimates and 90% CIs for geometric mean ratios were generated for Cmax, AUC0–∞, and AUC0–t.

Findings: Cmax and AUC met bioequivalence criteria for crushed tablets in water. Cmax and AUC decreased by 21.1% and 16.4%, respectively, with the lower bound of the CIs falling below the bioequivalence criteria for crushed tablets with applesauce. Similarly, administration of whole tablets with a high-fat, high-calorie meal reduced apixaban Cmax and AUC by 14.9% and 20.1%, respectively. The exposure reductions in both studies were considered not clinically significant.

Implications: Apixaban tablets can be administered crushed or whole, with or without food. The results of these alternative methods of administration support their use in patients who have difficulty swallowing tablets. ClinicalTrials.gov identifiers: NCT02101112 and NCT01437839. (Clin Ther. 2016;38:1674–1685) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: apixaban, bioavailability, crushed tablet, food effect, formulation, stability.
there is limited potential for drug-drug or drug-food interactions.\textsuperscript{16,21–27}

Certain patients, such as elderly individuals, young children, and some hospitalized patients, may be unable to swallow solid dosage forms. Pediatric patients <6 years of age may have difficulty swallowing adult dosage forms, and dysphagia is also a common potential complication of treatment in elderly patients.\textsuperscript{28–35} Patients with difficulty swallowing medication are more likely to delay or skip taking their medications entirely or seek alternate methods of administration. As a consequence, dysphagia is associated with a higher risk of medication errors.\textsuperscript{36} In these patients, in the absence of alternative formulations, mixing capsule contents or crushed tablets with semisolid foods or liquids is a common practice. However, extemporary manipulations of solid oral dose forms can alter the PK properties of the drug, and in some cases, relative bioavailability may be significantly affected. For example, the oral bioavailability of dabigatran etexilate mesylate increases by 75% when the pellets are taken without the capsule shell compared with the intact capsule formulation.\textsuperscript{37}

Apixaban is classified as a Biopharmaceutics Classification System Class III compound (high solubility/low permeability)\textsuperscript{38} and is nonionizable\textsuperscript{1,39}; thus, changes in pH do not affect the aqueous solubility of apixaban. Apixaban is available as small 2.5- and 5-mg film-coated tablets (the length of the 5-mg tablet is 9.73 mm; Bristol-Myers Squibb, data on file), which are expected to be relatively easy to swallow. However, there may still be patients who would benefit from apixaban but have difficulty swallowing an intact tablet. Therefore, a study evaluating the relative bioavailability of apixaban tablets after being crushed and mixed with different media was conducted.

In addition to the dosage form and patient-specific factors, such as weight, age, and renal function, various factors associated with how medication is administered can also affect PK properties; these factors include interactions with concomitant medications or food. For example, warfarin is known to have multiple drug-drug interactions and is susceptible to interaction with dietary components.\textsuperscript{40} Several studies have identified an effect of food on the PK properties of the factor Xa inhibitor rivaroxaban when administered after a high-carbohydrate or high-fat meal,\textsuperscript{41} and rivaroxaban prescribing information recommends that doses ≥ 15 mg be taken with food, whereas lower doses can be taken with or without food.\textsuperscript{42} A previous dedicated food effect study of apixaban found that the 90% CIs for both $C_{\text{max}}$ and AUC were entirely within the predetermined 80% to 125% equivalence interval, therefore indicating no clinically significant effect of food on apixaban PK properties.\textsuperscript{16} An additional food effect study was conducted using the marketed apixaban tablet formulation.

We report the results of the crushed tablet relative bioavailability study (study 1) and the commercial tablet food effect study (study 2). Furthermore, to support the administration of apixaban crushed tablets in liquid media or a soft-food vehicle, an assessment of apixaban stability was conducted to ensure that crushed tablets are stable in water, 5% dextrose in water (D5W), apple juice, and applesauce.

\section*{PARTICIPANTS AND METHODS}

\subsection*{Study Population}

Studies 1 and 2 included healthy adults, defined as those having no clinically significant deviation from normal in medical history, physical examination, ECGs, and clinical laboratory determinations and women of childbearing potential who had a negative serum pregnancy test result within 24 hours before starting the investigational product. In addition, participants in study 1 had to be 18 to 45 years of age, with a body mass index of 18 to 30 kg/m$^2$. Participants in study 2 had to be 21 to 45 years of age, with a body mass index of 17.5 to 30.5 kg/m$^2$. All participants were required to provide written informed consent before participation.

Individuals were excluded from either study for any history or evidence of abnormal bleeding, intracranial hemorrhage, or coagulation disorders, any GI surgery, or other conditions or comediations that could affect absorption of study drug, prescription drugs, over-the-counter medications or herbal preparations within 2 to 4 weeks of study commencement, or current or recent (within 3 months) GI disease, including, but not limited to, dyspepsia, GI ulcers, esophageal or gastric varices, hemorrhoids, or any known history of coexisting disease within the previous 6 months that may be associated with an elevated risk of bleeding.

\subsection*{Study Design}

The primary objectives of study 1 were to assess the bioavailability of apixaban crushed tablets suspended
in water or mixed with applesauce relative to apixaban whole tablets, all administered orally in healthy adults. Secondary objectives were to assess the safety and tolerability of apixaban and to assess the PK properties of apixaban crushed tablets when suspended in water or mixed with applesauce. The primary objective of study 2 was to evaluate the effect of food on apixaban PK properties after administration of single-dose apixaban commercial formulation tablets in healthy adults. The protocol for each study was approved by the independent review board of the site where the study took place, and both studies complied with all local regulations, the Declaration of Helsinki, and the International Conference on Harmonisation guidelines on Good Clinical Practice.

**Study 1**

Study 1 (NCT02101112) was an open-label, randomized, 3-treatment crossover study in healthy adults. Participants were admitted to the clinical facility on day 1 and remained at the clinical facility for the duration of the study. On day 1, participants were randomly assigned to 1 of 6 treatment sequences. All 3 treatments were composed of 10 mg of apixaban and 240 mL of water, with treatment C including an additional 30 g of applesauce (Table I). For each treatment period, apixaban was dosed immediately after a 10-hour overnight fast. Participants were not permitted to drink any additional water within 1 hour before or after dosing, with a 4-day washout period between treatments. A 10-mg (2 x 5-mg tablets) dose was selected because it is the highest approved dose of apixaban.

**Study 2**

Study 2 (NCT01437839) was an open-label, randomized, 2-treatment crossover study in healthy adults. Participants were admitted to the clinical facility on day 1 and remained at the clinical facility for the duration of the study. On day 1, participants were randomly assigned to 1 of 2 treatments and received the alternate treatment during the second study period. Both treatments were composed of 5 mg of apixaban and 240 mL of water, administered while the participant was in a fed or fasted state (Table I). A 5-mg dose was selected because it is the highest approved dose of apixaban.

**Table I. Study treatments.**

<table>
<thead>
<tr>
<th>Crushed tablet study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A (reference)</td>
<td>Apixaban tablets (2 x 5 mg) were administered whole with approximately 240 mL of water.</td>
</tr>
<tr>
<td>Treatment B</td>
<td>Apixaban tablets (2 x 5 mg) were gently crushed into a coarse particulate form (ie, not a fine powder) using a mortar and pestle, with the mortar and pestle rinsed with 30 mL of water, and the rinse solution used to suspend the crushed tablet in a dosing cup, with which the suspension was administered orally. The dosing cup was then rinsed with 30 mL of water, also administered orally, and the subject was provided with an additional 180 mL of water.</td>
</tr>
<tr>
<td>Treatment C</td>
<td>Apixaban tablets (2 x 5 mg) were gently crushed into a coarse particulate form (ie, not a fine powder) using a mortar and pestle and thoroughly mixed with 30 g of Mott’s applesauce in a dosing cup. The mortar and pestle were rinsed with 30 mL of water, and both the applesauce mixture and rinse solution were administered orally. Approximately 30 mL of water was used to rinse the rinse cup, spoon, and dosing cup, with the rinse solution administered orally and the subject provided with an additional 180 mL of water.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Food effect study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment A (reference)</td>
<td>Apixaban (1 x 5-mg tablet) was administered with approximately 240 mL of water.</td>
</tr>
<tr>
<td>Treatment B</td>
<td>Apixaban (1 x 5-mg tablet) was administered with approximately 240 mL of water after a high-fat, high-calorie breakfast.</td>
</tr>
</tbody>
</table>
approved apixaban tablet strength and was the highest approved dose at the time of study. For each treatment period, apixaban was dosed immediately after a 10-hour overnight fast or, in the case of the fed-state treatment, within 5 minutes of completing a high-fat, high-calorie breakfast (consisting of 2 fried eggs [large], 80 g of turkey bacon, 2 slices of white bread, 80 g of potato for hash browns, 45 g of butter [for cooking], and 240 mL of whole milk consumed within 30 minutes; total calories, 979 kcal, with 15%, 60%, and 25% from protein, fat, and carbohydrate, respectively) after a 10-hour fast. Participants were not permitted to eat or drink any additional water within 1 hour before or after dosing or to eat any additional food within the 4 hours after dosing, with a 5-day washout period between treatments.

**PK Assessments**

Blood samples (2.7 mL in 3.2% sodium citrate) for assessment of apixaban plasma concentrations were collected by venipuncture or indwelling catheter before dosing (0 hour) and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 24, 36, 48, 60, and 72 hours after dosing in study 1 and before dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 48, 60, and 72 hours after dosing in study 2. For both studies, apixaban concentration in human plasma was assayed using a validated liquid chromatography atmospheric pressure ionization tandem mass spectrometry method with a lower limit of quantification of 1 ng/mL during the period of known analyte stability (Intertek Pharmaceutical Services, El Dorado Hills, California).43

Apixaban PK parameters derived from plasma concentration–time profiles of apixaban included $C_{\text{max}}$, $AUC_{0-\infty}$, $AUC_{0-t}$, $T_{\text{max}}$, and $t_{1/2}$, using Phoenix WinNonlin, version 6.2.1 (Pharsight Corporation, St Louis, Missouri), in study 1 and using a Pfizer internally developed and validated software system, eNCA (electronic noncompartmental analysis), version 2.2.3 (Pfizer, New York, New York), in study 2. Point estimates and 90% CIs for geometric mean ratios were generated for comparison of $C_{\text{max}}$, $AUC_{0-\infty}$, and $AUC_{0-t}$ between each treatment and the reference treatment. In study 1, the relative bioavailability, defined as the ratio of test $AUC_{0-\infty}$ to reference $AUC_{0-\infty}$, was also derived. All statistical analyses were performed using SAS software, version 9.2 (study 2) or 9.3 (Study 1) (SAS Institute, Cary, North Carolina).

**Safety Profile Assessments**

Safety profile assessments for both studies were based on adverse event (AE) reports and results of vital sign measurements, physical examinations, 12-lead ECGs, and clinical laboratory tests performed at baseline and selected times throughout the study.

**Sample Size Calculations**

For study 1, the hypotheses were as follows: (1) there is no difference between the oral bioavailabilities of apixaban crushed tablets suspended in water relative to apixaban whole tablets, and (2) there is no difference between the oral bioavailabilities of apixaban crushed tablets mixed with applesauce relative to apixaban whole tablets. Similarity of bioavailability would be concluded if the 90% CIs for the ratio of geometric means of apixaban crushed tablets suspended in water or mixed with applesauce relative to apixaban whole tablets were wholly contained within 80% to 125% for $C_{\text{max}}$ and $AUC$. If there was no difference between the bioavailability of apixaban crushed tablets suspended in water relative to apixaban whole tablets, then data from 28 participants would provide approximately 98%, 99%, and 99% power to conclude similar bioavailability for $C_{\text{max}}$, $AUC_{0-\infty}$, and $AUC_{0-t}$, respectively. The overall power was 96% and 92% for both hypotheses, respectively. These calculations use the approach described by Diletti et al44 and assume $C_{\text{max}}$ and $AUC$ are log-normally distributed with intrapatient SD of 0.20 for ln$(C_{\text{max}})$ and 0.19 for ln$(AUC)$ (Bristol-Myers Squibb, data on file, 2008). To allow for possible dropouts, a total of 33 participants were randomly assigned to treatment.

For study 2, the hypothesis was that there was no difference between the oral bioavailability of apixaban when administered in a fed or fasted state. A sample size of 20 participants would provide 90% CIs for apixaban $C_{\text{max}}$ and $AUC$ for the difference between treatments of 88% to 113% and 92% to 109%, respectively, with 90% coverage probability. These calculations were based on estimates of intrapatient SD of 0.186 and 0.129 for ln$(C_{\text{max}})$ and ln$(AUC)$, respectively (Bristol-Myers Squibb, data on file, 2007). To allow for possible dropouts, 22 participants were randomly assigned to treatment.
**Stability Assessment**

Three different doses of apixaban (2.5 mg, 5 mg, and 2 × 5 mg) were tested for stability when suspended in water, D5W, or apple juice (Mott’s) and when mixed with applesauce (Mott’s). Tablets were gently crushed in a mortar and pestle and suspended in water, D5W, or apple juice or mixed with applesauce. The suspensions/mixtures were analyzed for potency and impurities at the initial time point (0 hour) and at 4 hours after incubation at 30°C and 75% relative humidity under normal room lighting.

**RESULTS**

**Demographic Characteristics and Disposition of the Study Participants**

A summary of demographic characteristics at baseline for all individuals randomly assigned to treatment is given in Table II for both studies. Study 1 was conducted at the Covance Clinical Research Unit Inc (Daytona Beach, Florida). A total of 33 healthy adults, comprising 21 white (64%), 8 black/African American (24%), 1 American Indian/Native Alaskan, and 3 other, were randomly assigned to treatment. A total of 31 of 33 individuals completed the study, with 1 individual (3%) withdrawn from the study because of AEs and 1 (3%) who withdrew consent to participate during the third treatment period. Study 2 was conducted at the Pfizer Clinical Research Unit in Singapore. All participants who enrolled in the study were Asian, and all but 4 participants were male. A total of 21 of 22 participants completed the study, with 1 (4.5%) withdrawing consent to participate during the second treatment period.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crushed tablet study (n = 33)</th>
<th>Food effect study (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean (SD) 32.3 (7.4)</td>
<td>31.2 (6.2)</td>
</tr>
<tr>
<td></td>
<td>Range 20-45</td>
<td>21-43</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td>Male 26 (79)</td>
<td>18 (82)</td>
</tr>
<tr>
<td></td>
<td>Female 7 (21)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Mean (SD) 26.1 (2.2)</td>
<td>23.6 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Range 20.3-29.9</td>
<td>19.1-29.1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Mean (SD) 77.4 (7.9)</td>
<td>69.2 (10.1)</td>
</tr>
<tr>
<td></td>
<td>Range 59.2-89.7</td>
<td>50.1-86.6</td>
</tr>
</tbody>
</table>

BMI = body mass index.

**PK Properties**

In study 1, the relative bioavailability of crushed tablets suspended in water or mixed with applesauce was 103% and 83.6%, respectively, compared with whole tablets (Table III). Apixaban mean Cmax and AUC were similar when administered as whole tablets or crushed tablets suspended in water, with Cmax, AUC0–t, and AUC0–∞ values meeting the predefined 80% to 125% bioequivalence criteria (Figure 1 and Table IV). When apixaban was administered as crushed tablets mixed with applesauce, apixaban Cmax and AUC0–∞ were 21% and 16% lower, respectively, than the corresponding values observed after administration of whole tablets, with the lower bound of the CIs for Cmax, AUC0–t, and AUC0–∞ falling outside the predetermined bioequivalence criteria (Figure 1 and Table IV). The median T_max of apixaban was 2 hours, regardless of the route of administration. The t1/2 was also unaffected by administration method, ranging from 12.2 to 12.5 hours (Figure 1 and Table III).

For study 2, when apixaban was administered under fed conditions, apixaban Cmax and AUC0–∞ were 15% and 20% lower, respectively, than the corresponding values observed after administration of apixaban under fasted conditions (Table IV). The median T_max of apixaban was 2 hours when administered in a fed state versus 3 hours when administered after an overnight fast. Mean t1/2 values for fed and fasted conditions were similar for both treatments (10.7 and 9.87 hours after fed and fasted apixaban administration, respectively) (Figure 2 and Table III).

**Safety Profile**

For study 1, there were no treatment-related serious AEs or bleeding-related AEs. AEs, all of which were considered mild, were reported for 3 individuals (9%). One participant was withdrawn from the study because of AEs (mild pruritus and
rash) considered by the investigator to be related to the study drug. These AEs were resolved with oral antihistamine and corticosteroid treatment. All other AEs were considered to be unrelated to the study drug. There were no clinically meaningful abnormalities in clinical laboratory values, vital signs, ECGs, or physical examinations.

For study 2, there were no deaths, serious AEs, or withdrawals from the study due to AEs, with all reported AEs categorized as mild and resolved without treatment. Two participants (9%) experienced treatment-related AEs under fasted conditions compared with 3 participants (14%) under fed conditions. The only treatment-related AE that occurred in >1 participant was headache, which was reported for 2 participants under fasted conditions. There were no clinically meaningful abnormalities in clinical laboratory values, vital signs, ECGs, or physical examinations.

### Stability Assessment

Apixaban was stable for 4 hours when the crushed tablet, equal to 2.5, 5, and 10 mg of apixaban, was suspended in water, D5W, or apple juice or when mixed with applesauce and incubated at 30°C/75% relative humidity under room lighting (Supplemental Table 1). There was at least 95.8% of the stated label claim dose present after the 4-hour incubation period for all doses and media tested.

<table>
<thead>
<tr>
<th>Study</th>
<th>C(_{\text{max}}), GM (%CV), ng/mL</th>
<th>AUC(_{0-\infty}), GM (%CV), ng·h/mL</th>
<th>AUC(_{0-t}), GM (%CV), ng·h/mL</th>
<th>T(_{\text{max}}), Median (Range), h</th>
<th>t(_{1/2}), Mean (SD), h</th>
<th>F(_{\text{rel}}), GM (CV%), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crushed tablet study (n = 33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A) 2 × 5-mg apixaban tablets (n = 32)</td>
<td>233 (27)</td>
<td>2443 (27)</td>
<td>2406 (27)</td>
<td>2.00 (1.00–5.00)</td>
<td>12.4 (5.4)</td>
<td>-</td>
</tr>
<tr>
<td>(B) 2 × 5-mg apixaban tablets crushed and suspended in 30 mL of water (n = 33)</td>
<td>249 (23)</td>
<td>2528 (22)</td>
<td>2488 (22)</td>
<td>2.00 (0.58–4.00)</td>
<td>12.2 (5.2)</td>
<td>103 * (24)</td>
</tr>
<tr>
<td>(C) 2 × 5-mg apixaban tablets crushed and mixed with 30 g of applesauce (n=32)</td>
<td>185 (23)</td>
<td>2044 (22)</td>
<td>2003 (23)</td>
<td>2.00 (1.00–4.00)</td>
<td>12.5 (5.1)</td>
<td>83.6 (20)</td>
</tr>
<tr>
<td>Food effect study (n = 22)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(A) 1 × 5-mg apixaban tablet administered in a fasted state (n = 22)</td>
<td>121.3 (28)</td>
<td>1229 (22)</td>
<td>1200 (23)</td>
<td>3.00 (1.00–6.00)</td>
<td>9.87 (2.35)</td>
<td>-</td>
</tr>
<tr>
<td>(B) 1 × 5-mg apixaban tablet administered following a high-fat, high-calorie meal (n = 22)</td>
<td>103.2 (20)</td>
<td>971.6 (21)</td>
<td>937.6 (22)</td>
<td>2.00 (0.917–4.02)</td>
<td>10.7 (2.97)†</td>
<td>-</td>
</tr>
</tbody>
</table>

F\(_{\text{rel}}\) = relative bioavailability; GM = geometric mean.

*\(n = 32\).

†\(n = 21\).
DISCUSSION

In study 1, administration of apixaban as crushed tablets suspended in water met the bioequivalence criteria, with the geometric mean ratios for C\text{max} and AUC close to unity and the 90% CIs contained within the 0.8 to 1.25 boundary, indicating that administration of the tablet in this manner does not affect the extent of apixaban absorption. This finding is consistent with previous studies reporting that there is comparable bioavailability between apixaban tablets and an apixaban oral solution and comparable bioavailability between an apixaban oral solution and crushed tablets suspended in D5W and administered through a nasogastric tube.45 A limitation of this study and of the previous experience is that tablets were crushed using a mortar and pestle and a rinse procedure was followed. In clinical practice, methods for crushing tablets may vary. As with any extemporaneous compounding, care is needed to avoid loss of drug and to ensure the full dose of the drug is administered. As long as such care is taken, the results of this study, along with previous study results, indicate that crushed apixaban tablets suspended in fluids such as water is an acceptable method of apixaban administration.

Unlike administration of crushed tablets suspended in water, administration of crushed apixaban tablets mixed in applesauce did not result in equivalent exposure to whole apixaban tablets after fasted administration. As we have found, apixaban is stable in applesauce for at least 4 hours; therefore, loss of drug due to instability in applesauce is not a factor because the entire dose was consumed within the stability window. Applesauce or apple juice can inhibit human organic anion transporters46; however, apixaban is not a substrate for organic anion transporter (Bristol-Myers Squibb, data on file). Apixaban is a substrate of P-glycoprotein and breast cancer resistance protein,2e flux transporters located in the intestine, although consumption of applesauce or apple juice is not known to influence P-glycoprotein or breast cancer resistance protein function. In addition, these transporters are efflux transporters, and inhibiting their function would tend to increase bioavailability.47 Therefore, the reduced apixaban exposure in the presence of applesauce is not likely to be transporter mediated.

In contrast, the food effect findings reported here indicate that apixaban exposure was lower after coadministration with food, whereas the previous food effect study found a slightly higher apixaban
exposure (10% higher for $C_{\text{max}}$ and 4% higher for $AUC_{0-\infty}$) in the presence of food. The findings of the crushed tablet study and the food effect study are consistent, however, with findings after administration of an apixaban oral solution with infant formula or Boost Plus (Nestlé, Vevey, Switzerland) (19%–32%
decrease in C\text{max} and 8\%–19\% decrease in AUC\text{0–\infty}.\textsuperscript{45} The difference between the effect of food in the original food effect study and these more recent evaluations is unclear. Nonetheless, the Phase II tablet formulation used in the original food effect study has similar dissolution characteristics to that of the final, commercial formulation and met the in vitro dissolution criteria for equivalence (Bristol-Myers Squibb, data on file, 2006). In addition, comparable bioavailability between the formulations was found in a relative bioavailability study (Bristol-Myers Squibb, data on file, 2007).

In general, a negative food effect is most likely to occur for Biopharmaceutics Classification System Class III drugs, such as apixaban, particularly if food interacts with drug absorption.\textsuperscript{48,49} Different mechanisms have been postulated. For example, an increase in viscosity of the dissolution fluid particularly affects the absorption of Biopharmaceutics Classification System Class III compounds that have preferential absorption in the upper GI tract if the drug release from the dosage form is delayed.\textsuperscript{50} However, apixaban exposure is reduced regardless of formulation in the presence of food (including high-fat, high-calorie meal, infant formula, nutritional drink, and applesauce); therefore, the viscosity of the intestinal content may not be the explanation. It is possible that the decrease in exposure is due to change in GI transit time with food consumption, therefore decreasing the fraction of the dose available for absorption.\textsuperscript{51} In the study by Penrod et al,\textsuperscript{52} persistent subtherapeutic prothrombin times were observed in 2 case studies in which warfarin was administered through a nasogastric tube with a nutritional supplement. The authors suggested that this could be attributable to binding between warfarin and the nutritional supplement components. In a follow-up in vitro experiment in which binding between Boost Plus and apixaban was measured, similar binding was observed for apixaban (Bristol-Myers Squibb, data on file, 2015). Therefore, nonspecific binding to certain nutritional supplement components may be one of the explanations for reduced apixaban exposure in the presence of Boost Plus and a high-fat meal.

It is evident that the effect of food, if any, on apixaban exposure is minimal because the effect of food on apixaban exposure across these studies was a decrease of \(\leq 20\%\). Approximately 35,600 patients have been treated with apixaban in 15 completed Phase II and Phase III clinical trials spanning several different patient populations, with apixaban administered twice daily without regard to meals in all those studies. Considering the favorable benefit-risk profile observed in the Phase III studies,\textsuperscript{3–9} any apparent effect of food on apixaban exposure does not have a clinically relevant effect; thus, apixaban is administered with or without food in clinical practice. Therefore, given the modest effect of crushing and mixing apixaban tablets with applesauce on apixaban exposure, this method of administration may represent a viable alternative for patients who have difficulty swallowing. Apixaban was generally well tolerated in both of the studies presented here, and there were no unexpected tolerability issues raised regardless of treatment received.

CONCLUSION

Apixaban bioavailability was comparable between whole tablets and crushed tablets suspended in water; these results support crushed tablets suspended in water as a viable method of administration in patients who are unable to swallow solid dosage forms. Although administration of crushed apixaban tablets mixed with applesauce and administration of apixaban tablets with a high-fat, high-calorie meal resulted in a somewhat decreased apixaban exposure, the effect was small and considered not clinically relevant. Overall, these results support the use of crushed tablets as an appropriate method of apixaban administration in patients who have difficulty swallowing whole tablets and indicate that apixaban can be taken with or without food.

FUNDING SOURCES

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Bristol-Myers Squibb and Pfizer. Dr. Song and Mr. Suzuki participated in conception of the work, design of the work, acquisition of data, analysis of data, interpretation of data, drafting of the work, revising the work critically for important intellectual content, and final approval of the version to be published. Drs. Chang, R.J.A. Frost, Kelly, LaCreta, and C. Frost participated in interpretation of the data, revising the work critically for important intellectual content, and final approval of the version to be published.

CONFLICTS OF INTEREST
All authors are employees of Bristol-Myers Squibb or Pfizer and received salaries and benefits commensurate with employment. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIAL
Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.05.004.

REFERENCES


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**Supplementary Material**

**Table SI.**

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Medium</th>
<th>% Label Claim at Stability Time Point</th>
<th>T = 0 h</th>
<th>T = 4 h*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mg</td>
<td>Water</td>
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*Apixaban crushed tablets were incubated in selected media for 4 hours at 30°C and 75% relative humidity.