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 C_{max}, $AUC_{0-\infty}$, and AUC_{0-t}.

Findings: C_{max} and AUC met bioequivalence criteria for crushed tablets in water. C_{max} 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 C_{max} 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;▮:▮▮▮–▮▮▮)

Key words: apixaban, bioavailability, crushed tablet, food effect, formulation, stability.

INTRODUCTION

The oral, selective, direct, reversible factor Xa inhibitor apixaban[1,2] is approved in the European Union, United States, and many other countries to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation,[3,4] for thromboprophylaxis after elective hip or knee replacement surgery,[5–7] for the treatment of deep vein thrombosis or pulmonary embolism,[8] and to reduce the risk of recurrent venous thromboembolism after an initial thromboembolic event.[9] Apixaban is an immediate-release tablet formulation with rapid dissolution (at least 80% dissolved within 30 minutes) and pH-independent aqueous solubility. Apixaban has predictable pharmacokinetic (PK) properties, and exposure is dose proportional for the approved dose range of 2.5 to 10 mg.[10–16] The bioavailability of apixaban is approximately 50%,[17] and it is absorbed primarily in the upper gastrointestinal (GI) tract, proximal to the colon.[18] Peak apixaban plasma concentration is reached approximately 3 hours after oral administration in healthy adults, with a mean elimination $t_{½}$ of approximately 12 hours.[12] Elimination occurs via multiple pathways, including metabolism, renal elimination of unchanged drug, and excretion into the intestinal tract.[19,20] In addition to having a pharmacologic profile consistent with twice-daily dosing,

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there is limited potential for drug-drug or drug-food interactions.[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.[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.[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.[37]

Apixaban is classified as a Biopharmaceutics Classification System Class III compound (high solubility/low permeability)[38] and is nonionizable[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.[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,[41] and rivaroxaban prescribing information recommends that doses ≥15 mg be taken with food, whereas lower doses can be taken with or without food.[42] A previous dedicated food effect study of apixaban found that the 90% CIs for both C_{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.[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.

PARTICIPANTS AND METHODS

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 comedications 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.

Study Design

The primary objectives of study 1 were to assess the bioavailability of apixaban crushed tablets suspended