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Can Acalabrutinib Be Prepared as a Liquid Formulation?

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Introduction: The oral Bruton tyrosine kinase inhibitor acalabrutinib (Calquence®) was approved by the Food and Drug Administration (FDA) in 2017 as a 100 mg capsule formulation for the treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma, as well as adult patients with untreated or previously treated mantle cell lymphoma. Acalabrutinib was initially available only as a capsule formulation. The solubility of acalabrutinib capsules was pH-dependent, with reduced solubility observed as gastric pH increased. Consequently, drug exposure decreased when acalabrutinib capsules were co-administered with medications that increased gastric pH, such as proton pump inhibitors (PPIs), H2-blockers, or antacids; therefore, concomitant use was not recommended.

New Tablet Formulation: In 2022, a new tablet formulation of acalabrutinib was FDA-approved, and the capsule formulation was later discontinued. The film-coated 100 mg tablet was easier to swallow and approximately 50% smaller in size than the capsule. Although the prescribing information for the tablet formulation states that acalabrutinib maleate has pH-dependent solubility, being freely soluble in water at pH values below 3 and practically insoluble at pH values above 6, studies have demonstrated that the new tablet formulation has pH-independent drug release. Furthermore, the package insert for the tablet formulation does not include interactions with medications that alter pH (e.g., antacids, H2-blockers, PPIs), and drug-drug interactions resources, such as UpToDate® Lexidrug™, indicate that this interaction is specific to the capsule formulation.

Recommended Dosage Regimen: The recommended dosing regimen of acalabrutinib generally targets a total daily dose of 200 mg, administered as one 100 mg tablet every 12 hours. Prescribing information advises against chewing, crushing, dissolving, or cutting the tablets. At present, no commercially available liquid formulation exists necessitating tablet manipulation for patients who are unable to swallow tablets or require nasogastric (NG) tube administration. Studies exploring the feasibility of preparing a liquid formulation are provided below.

Capsule Study: Sharma and colleagues conducted a phase 1, open-label, crossover study evaluating the bioavailability of NG tube-administered acalabrutinib capsules formulated as a suspension in regular, degassed Coca-Cola compared to the orally administered capsules. Of note, Coca-Cola which contains phosphoric acid, was used to enhance acalabrutinib's solubility. Additionally, the pharmacokinetic effect of a PPI on the absorption of the acalabrutinib suspension was also assessed. The study consisted of three treatment periods in which participants (N=35) received a single dose of: treatment A (100 mg of prepared acalabrutinib suspension plus 20 mg rabeprazole), treat-

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ment B (100 mg of prepared acalabrutinib suspension), or treatment C (100 mg acalabrutinib capsule administered orally with water). The results demonstrated that the systemic exposure or area under the curve (AUC) of acalabrutinib and its active metabolite following NG tube administration of the suspension was comparable to that observed after oral administration of the capsule. However, the rate of absorption of acalabrutinib was faster when administered as an NG suspension than when administered as an oral capsule. Additionally, the study demonstrated that the impact of PPI coadministration on the pharmacokinetics of acalabrutinib and its active metabolite was mitigated by the acidity of Coca-Cola, and the AUC following NG tube administration of the acalabrutinib suspension was comparable in both the presence and absence of a PPI. The authors concluded that the contents of an acalabrutinib capsule suspended in Coca-Cola administered through an NG tube had bioavailability similar to that of the oral capsule and could be co-administered with PPIs.

Tablet Study: Sharma and colleagues reported a series of three, phase 1 single-dose, randomized, crossover studies conducted in healthy volunteers. In Study 1, participants (N=30) were randomized to one of four dosing sequences, each receiving acalabrutinib tablets (AT) then acalabrutinib capsules (AC) (or the reverse sequence), followed by AT administered with either a PPI or food, with a 7-day washout period between each dosing sequence. The tablet formulation exhibited pH-independent release relative to the capsule formulation with no significant impact on bioavailability when administered concomitantly with a PPI or food. Study 2 evaluated the bioequivalence of AT and AC, with participants (N=66) randomized to receive AT followed by AC or AC followed by AT, separated by a ≥ 5-day washout period. Analyses demonstrated comparable AUC values, confirming bioequivalence between the two formulations. Study 3 then evaluated the bioavailability of acalabrutinib tablets when administered as a suspension via an NG tube in the presence of a PPI. Participants (N=20) in Study 3 received through an NG tube either a suspension prepared from an acalabrutinib tablet dispersed in water (AT-NG), followed by a suspension prepared from an acalabrutinib capsule in a Coca-Cola-simethicone mixture (simethicone was used to decrease foaming) (AC-NG) or the AC-NG suspension followed by the AT-NG suspension; there was a ≥4-day washout period between treatments. After the second washout period, all participants received the AT-NG suspension co-administered with a PPI . The systemic exposure of acalabrutinib and its active metabolite was similar when the acalabrutinib tablet was administered as a suspension via NG tube compared with the oral administration of the tablet. Additionally, the relative bioavailability was of the AT-NG and AC-NG suspensions was comparable. Finally, co-administration of a PPI with the AT-NG suspension did not have a significant effect on systemic absorption. The directions for the preparing the acalabrutinib tablet suspension are listed below.

Preparation of acalabrutinib tablet suspension for NG tube administration:

1. Carefully place an acalabrutinib tablet in a bottle.
2. Add 15 mL of room-temperature water to the bottle and secure the cap.
3. Agitate by shaking the bottle for 150 seconds until the tablet is fully dispersed.
4. Flush the NG tube and the enteral syringe with 15 mL of water before administration, then transfer the entire suspension from the bottle directly into the enteral syringe for administration.
5. Rinse the bottle twice with an additional 15-mL aliquot of water and add each rinse to the enteral syringe for administration.
6. Flush the NG tube with 15-30 mL of water.
7. Recap the NG tube.

Conclusion: A Phase 1 study demonstrated that the bioavailability of the acalabrutinib tablet oral suspension was comparable to that of the oral tablet dosage form. Since acalabrutinib tablets exhibited pH-independent solubility, both the tablet and tablet suspension may be administered concomitantly with PPIs.

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