

In This Issue

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Prepared as a
Liquid Formulation?



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Can Venetoclax Be Prepared as a Liquid Formulation?

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Introduction: Venetoclax (Venclexta®) is an oral, selective inhibitor of the anti-apoptotic protein B-cell lymphoma-2 (BCL-2) indicated for the treatment of adults with hematologic malignancies. It is approved by the Food and Drug Administration (FDA) for the treatment of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and in combination with other agents for certain patients with acute myeloid leukemia (AML). Venetoclax is available as a film-coated tablet in 10 mg, 50 mg, and 100 mg strengths. Treatment regimens typically involve a gradual dose-escalation schedule during initiation, particularly for patients with CLL/SLL, to reduce the risk of tumor lysis syndrome. According to the prescribing information, venetoclax tablets should be swallowed whole and should not be chewed, crushed, or broken prior to administration. However, due to the large size of the 100 mg venetoclax tablets, use in the pediatric population and those with dysphagia may be problematic. Currently, no commercially available venetoclax oral suspension exists and despite its poor aqueous solubility, tablet manipulation may be required to create a liquid preparation. Studies exploring the feasibility of crushing venetoclax tablets and dispersing them in water or various vehicles (e.g., apple juice, applesauce, yogurt) are summarized below.

Pharmacokinetic Studies: Bandawi and colleagues conducted a phase 1 study involving the interchangeability of venetoclax lower-strength tablets

and newly developed oral powder formulations with the 100 mg venetoclax tablet. The bioavailability of the venetoclax 10 mg and 50 mg tablets relative to a 100 mg tablet, as well as of the oral powder formulations administered using different vehicles (apple juice, applesauce, and yogurt) compared to their dispersion in water was evaluated. The 100 mg dose of venetoclax demonstrated bioequivalence to the same dose using 10 mg or 50 mg tablets. The areas under the curve (AUCs) of the 0.72% and 7.2% oral powder formulations of venetoclax administered with apple juice, applesauce, and yogurt were comparable to the AUCs of the powder formulations dispersed in water. This study suggested that the oral powder formulations of venetoclax had bioavailability similar to the 100 mg tablet and could be used in the future to deliver therapeutic doses of venetoclax to patients with dysphagia. Of note, a powder formulation of venetoclax is not currently commercially available. Alaei and colleagues conducted a phase I randomized, three-way, cross-over, bioavailability study to evaluate the pharmacokinetics, stability, and safety of crushed and ground venetoclax 100 mg tablets compared with intact tablets in 15 healthy participants. The main objective was to determine whether tablet manipulation affected venetoclax exposure. Participants received crushed, ground, or intact venetoclax tablets on day 1 of each period with 240 mL of water 30 minutes after a high-fat break-

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fast. In the study, venetoclax tablets were manipulated using these two methods:

1. Crushed tablets: Tablets were manually crushed using a pill crusher to produce a coarse powder with a broad particle size distribution.
2. Ground tablets: Tablets were processed using an automated pill crusher which ground the tablets into a finer powder.

The prepared powder of the crushed and ground tablets was transferred to an amber pharmacy vial and stored at room temperature (15-25°C or 59-77°F) and <60% relative humidity before administration. On dosing days, participants took the crushed, ground, or intact tablets by mouth directly from the vial followed by a glass of water within 30 minutes of breakfast. Participants were divided into three groups of five. Each group received all three presentations of the medication sequentially with a 5-day washout period between each dosage form (crushed, ground, intact tablet) to minimize drug carryover given its 24-hour half-life. Blood samples were collected over 72 hours to measure venetoclax plasma concentrations and determine pharmacokinetic parameters, including maximum concentration (C_{max}), time to peak concentration (T_{max}), and AUC. The study showed that overall systemic exposure, as represented by the AUC, was comparable between intact and manipulated tablets. The AUCs of intact, crushed, and ground tablets were 10.2 mcg x h/mL, 10.1 mcg x h/mL, and 10.4 mcg x h/mL respectively. The maximum plasma concentrations were modestly lower with manipulated tablets, but the differences were not considered clinically meaningful. Additionally, the T_{max} (approximately 6 hours) and elimination half-life (approximately 12–14 hours) were similar across intact, crushed, and ground tablet formulations. Stability studies showed no change in physical appearance or chemical properties of crushed or ground tablets stored in amber pharmacy vials with closed snapped caps at room temperature for 72 hours. The authors concluded that these results suggest no clinically meaningful changes in bioavailability or stability when venetoclax tablets were crushed or ground and crushing before administration may be considered for patients with swallowing difficulties. For ease of administration, they stated that the crushed tablet may be mixed with apple juice, applesauce, or yogurt.

Feeding Tube Study: Sato and colleagues presented a case in which crushed venetoclax tablets were administered through a percutaneous endoscopic gastrostomy (PEG) tube in a patient with relapsed Japanese AML due to esophageal stricture. Plasma concentrations of crushed venetoclax tablets administered via a PEG tube showed T_{max}, C_{max}, and AUC values comparable to the previously reported pharmacokinetic parameters of intact venetoclax tablets. No unexpected adverse events were reported. This case suggests that administration of crushed venetoclax tablets may be a safe option for patients with a PEG tube.

Other Considerations: Despite the available evidence supporting tablet manipulation, some practical and safety factors to consider are:

1. Venetoclax tablets are not labeled for crushing or dispersion in the prescribing information, and feeding tube administration is not well studied.
2. There are no data regarding feeding tube occlusion by crushed venetoclax tablets, which poses a safety risk that should be considered.
3. Venetoclax is an antineoplastic agent with reproductive risk, so appropriate hazardous drug handling precautions should be taken when manipulating the tablets.

Conclusion: While studies have evaluated the pharmacokinetic parameters of crushed venetoclax tablets, clinical trials are needed to confirm the therapeutic efficacy of this altered dosage form. However, when patients cannot swallow venetoclax tablets, crushing and administering them with water or suspending them in apple juice, applesauce, or yogurt can be considered. Additionally, some evidence supports PEG tube administration of crushed venetoclax tablets.

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