Roy Guharoy, PharmD, MBA, FCP, FCCP, FASHP
Department of Pharmacy
Baptist Health
Montgomery, AL

University of Massachusetts Medical School
Montgomery, AL
Rguharoy@baptistfirst.org

Edward Krenzelok, PharmD, FAACT, DABAT, FEAPCCT
School of Pharmacy
University of Pittsburgh
Pittsburgh, PA

DOI 10.1093/ajhp/zxab053

On crushing of deutetrabenazine tablets

We read with interest the case report on use of crushed deutetrabenazine for treatment of tardive dyskinesia in a patient with severe orofacial symptoms by Wietholter et al.[1] Although the authors report that the patient had a safe and effective response to deutetrabenazine, as Teva Pharmaceutical Industries considers patient safety a top priority, we would like to clarify important points related to crushing of deutetrabenazine tablets marketed in the United States as Austedo tablets. In the article, the authors do not suggest a particular concern about the safety of crushing deutetrabenazine, despite the fact that the effects of crushing have not been studied, and they also imply that they received a similar impression from Teva Medical Information. Please see the text below from the article by Wietholter et al and the phrase we have italicized.

> As the patient was unable to tolerate any oral challenge and required enteral administration, the primary manufacturer, Teva Pharmaceutical Industries Ltd, was contacted to determine the feasibility of administering the medication via a crushed modality. The manufacturer responded that although use of the medication in crushed form had not been studied, *there was little reason to suspect harm might result from administration in that manner*.

We are concerned that the information in the article may be misleading, as readers may interpret that Teva endorsed crushing the tablet and/or that the formulation is amenable to alteration. As described in section 2.1 of the prescribing information, the deutetrabenazine tablet should be "swallowed whole, do not chew crush or break tablets."[2] We wish to clarify that the Teva Medical Information response to the authors was that crushed deutetrabenazine has not been studied. The authors received this information verbally and were also mailed a medical information summary on dosing and administration, including statements addressing lack of information on administration via nasogastric tubes and other forms of oral bypass administration. The Teva Medical Information response also stated that the effects of chewing, crushing, or breaking tablets are unknown. Please see the additional text below from the article by Wietholter et al, which we have italicized.

> *Given deutetrabenazine tablets' lack of enteric coating or materials that might cause a nonintact dosage form to have long-acting effects, none of the listed contents were expected to be altered when crushed and dissolved in water.*

In clarification of the formulation, deutetrabenazine tablets contain excipients and have physical characteristics, such as dissolution profile, that are not characteristic of immediate-release products.[3] The safety and efficacy of deutetrabenazine was established in registration trials using tablets with this specific pharmacokinetic profile. As a result, and without data as noted above, it is possible that alteration of the tablet formulation (eg, crushing) could affect the pharmacokinetic profile. This could potentially lead to adverse events or affect the expected effectiveness.

In summary, we submit this letter to indicate potential misinterpretations contained in this case report and to emphasize that alteration of deutetrabenazine tablets could plausibly cause untoward effects. Per the US labeling information, which is based on the formulation, deutetrabenazine tablets should be taken whole.

1. Wietholter JP, Sizemore J, Piechowski K. Crushing deutetrabenazine for treatment of tardive dyskinesia in a patient with severe orofacial symptoms: a case report. *Am J Health-Syst Pharm.* 2020;77(18):1477-1481.
2. Austedo. Package insert. Teva Pharmaceuticals USA, Inc.; revised December 2020. https://www.austedo.com/globalassets/austedo/prescribing-information.pdf
3. Center for Drug Evaluation and Research, US Food and Drug Administration. Application number 208082-Orig1s000. Chemistry review. Electrically signed March 2, 2017. Accessed December 17, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208082Orig1s000ChemR.pdf

Helena Knebel, MD
Medical Scientific Unit
Global Research and Development
Teva Pharmaceutical Industries, Ltd
Netanya, Israel
Helena.Knebel@teva.co.il

Jessica Alexander, PhD
Global Research and Development
Teva Pharmaceutical Industries, Ltd
West Chester, PA

Amanda Wilhelm, PhD
Global Research and Development
Teva Pharmaceutical Industries, Ltd
West Chester, PA

Pippa Loupe, PhD
Global Research and Development
Teva Pharmaceutical Industries, Ltd
West Chester, PA

Frank Schneider, PhD
Global Research and Development
Teva Pharmaceutical Industries, Ltd
Ratiopharm GmbH, Ulm, Germany

Mark Forrest Gordon, MD
Global Research and Development
Teva Pharmaceutical Industries, Ltd
West Chester, PA

Disclosures: All authors are employees in the Global Research and Development Division of Teva Pharmaceutical Industries, Ltd.

Keywords: Austedo, chorea, crushing, deutetrabenazine, tardive dyskinesia

DOI 10.1093/ajhp/zxab130

Crushing of deutetrabenazine tablets limited to individual case

Recently, there has been criticism, including a commentary by Knebel et al in the *Journal*, about our case report on crushing of deutetrabenazine tablets. In the report, we recounted an experience with the administration of crushed deutetrabenazine via percutaneous endoscopic gastrostomy tube to a patient who was unable to swallow pills due to extensive orofacial dyskinesia.[1] While we acknowledge the concerns that readers may misinterpret our report as an endorsement of crushing deutetrabenazine from the manufacturer, we do not agree that the case was represented as such. We mentioned that deutetrabenazine should be swallowed whole and agree that this should be the dosing modality recommended, barring any further studies. However, as discussed in the case report, due to the severity of the clinical presentation, our intervention was an attempt to improve quality of life for a patient who presented with a clinical scenario that had limited options for treatment. After weighing the risks and benefits of our intervention, we believe we acted in the best interest of the patient, given that we were able to closely monitor for efficacy and toxicity that might emerge as a result of administration of crushed deutetrabenazine.

The manufacturer did not weigh in on our risk-benefit discussion or promote crushing the medication, and the case report represents the opinions and conclusions of the authors alone. Subsequently, we reported the details of our successful experience, noting that further studies are needed before this intervention can be applied to other patients. Since our experience was outside the published literature, we felt it was important to share our findings.

1. Wietholter JP, Sizemore J, Piechowski K. Crushing deutetrabenazine for treatment of tardive dyskinesia in a patient with severe orofacial symptoms: a case report. *Am J Health-Syst Pharm.* 2020;77(18):1477-1481. doi:10.1093/ajhp/zxaa205.

Jon P. Wietholter, PharmD, BCPS, FCCP
West Virginia University (WVU) School of Pharmacy
WVU–Medicine Ruby Memorial Hospital
Department of Clinical Pharmacy
Morgantown, WV
jwietholter@hsc.wvu.edu

Jenna Sizemore, MD
West Virginia University School of Medicine
Department of Medicine
Morgantown, WV

Kara Piechowski, PharmD, BCPS
WVU–Medicine Ruby Memorial Hospital
Department of Pharmacy
Morgantown, WV