Important Drug Safety Notice

TO ALL PARTICIPATING PHARMACIES

Circular Letter MC23-051-CG
September 22, 2023

FDA announced that based on new data, the U.S. Food and Drug Administration is changing the therapeutic equivalence rating for tacrolimus oral capsule products manufactured by Accord Healthcare Inc. under abbreviated new drug application 091195 from AB to BX. A BX rating means that the data are insufficient to show that Accord Healthcare Inc.'s tacrolimus oral capsules provide the same therapeutic effect as Prograf (tacrolimus) oral capsules. This means that Accord Healthcare Inc.'s tacrolimus oral capsules are still FDA-approved and can be prescribed, but are no longer recommended as automatically substitutable at the pharmacy (or by a pharmacist) for Prograf (tacrolimus) oral capsules. Oral capsules from other manufacturers and other tacrolimus dosage forms are not affected by this issue. Potential harms to patients from higher concentrations of tacrolimus include kidney damage (nephrotoxicity); high blood pressure (hypertension); nerve damage (neurotoxicity), such as seizures, tremors, or headache; and elevated potassium levels (hyperkalemia). However, FDA is not aware of post-marketing issues regarding safety or efficacy for Accord Healthcare Inc.'s tacrolimus oral capsules.

RECOMMENDATIONS

1. Pharmacies should review their currently available tacrolimus inventory and ensure that their personnel is aware of this change in therapeutic equivalence rating.

2. Patients can determine the manufacturer of their tacrolimus oral capsules by contacting their pharmacy. Patients currently taking Accord Healthcare Inc.'s tacrolimus oral capsules should not make changes to their treatment, except in consultation with their health care professional.

3. Patients should also inform their health care professional if they have experienced any problems that may be related to taking Accord Healthcare Inc.'s tacrolimus oral capsules.

4. Expect patients to visit your pharmacy asking for information on this safety issue and prepare your pharmacy staff on how to handle the situation.

MC-Rx Pharmacy Services Department

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FDA is changing the therapeutic equivalence rating for Accord Healthcare Inc.'s generics of Prograf (tacrolimus) oral capsules

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[9/18/2023] Based on new data, the U.S. Food and Drug Administration is changing the therapeutic equivalence rating for tacrolimus oral capsule products manufactured by Accord Healthcare Inc. under abbreviated new drug application 091195. These drugs are indicated for the prevention of organ rejection in adult patients receiving kidney, liver, or heart transplants, and in pediatric patients receiving liver transplants.

FDA is concerned that the peak blood concentration of tacrolimus for Accord Healthcare Inc.'s generic tacrolimus oral capsules may be increased compared to the brand-name drug, Prograf (tacrolimus), creating a risk of toxicity. However, according to the new data, there were no significant differences in the trough blood levels, indicating no increased risk for organ rejection.

In 2011, FDA determined that tacrolimus products qualified as narrow therapeutic index drugs, and in 2012, updated recommendations for the design of bioequivalence studies to support therapeutic equivalence for tacrolimus generics. This change led to concerns from the transplant community regarding the substitutability of FDA-approved generic tacrolimus oral capsules that were approved prior to 2012, for both their therapeutic equivalence to the brand-name drug, Prograf (tacrolimus) and other approved generics. FDA funded a number of studies to investigate these concerns. Multiple post-approval studies signaled a potential issue with the bioequivalence of Accord Healthcare Inc.'s tacrolimus oral capsules and this led FDA to fund an additional study by BioPharma Services USA. FDA reviewed the results of the bioequivalence study by BioPharma along with other evidence. These studies indicate that Accord Healthcare Inc.'s tacrolimus oral capsules may deliver drug to the body at a higher maximum concentration compared to Prograf's tacrolimus oral capsules. The increased peak concentration may result in patients having too much tacrolimus in their body compared to Prograf, which may result in signs or symptoms of tacrolimus toxicity **(see Figures 1–3).**

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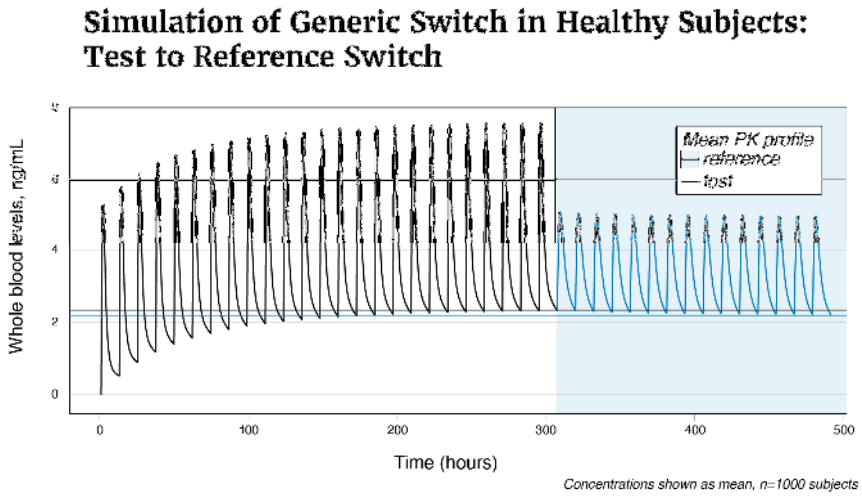

Figure 1. *Based on the tacrolimus whole blood levels after a single dose oral administration of Accord (test) and Prograf (reference) tacrolimus oral capsules, a simulation was conducted to demonstrate the impact of switching a subject stabilized on Accord (as determined by the achievement of steady state with multiple subsequent doses of Accord every 12 hours) to Prograf.*

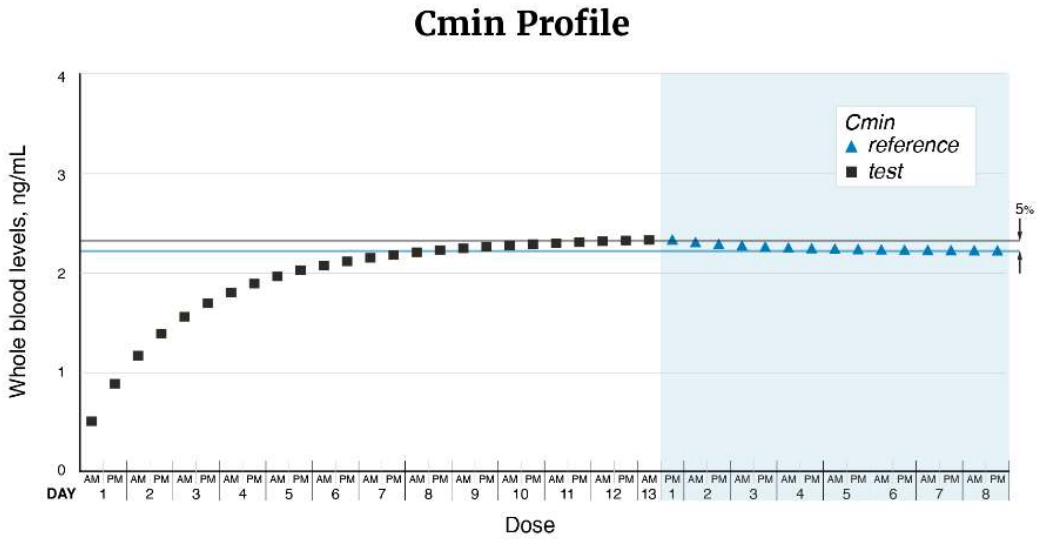

Figure 2. *From Figure 1, the minimum tacrolimus whole blood levels (or C^{min} or the trough concentration) after each dose of Accord (test) and Prograf (reference) tacrolimus oral capsules (i.e., the concentration at 12 hours when the subsequent dose is given). Horizontal lines represent the steady state C^{min} value for each treatment.*

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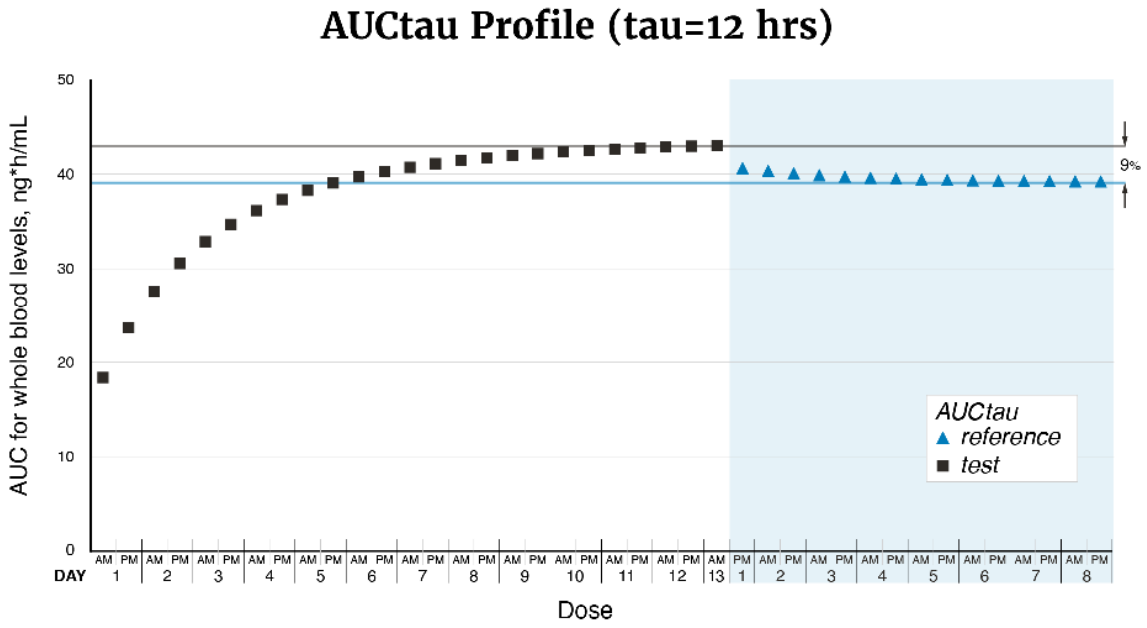

***Figure 3**. From Figure 1, the overall area-under-the-curve associated with each dose of Accord (test) and Prograf (reference) tacrolimus oral capsules (or AUC^{tau} where tau is 12 hours). Horizontal lines represent the steady state AUC^{tau} value for each treatment.*

Potential harms to patients from higher concentrations of tacrolimus include kidney damage (nephrotoxicity); high blood pressure (hypertension); nerve damage (neurotoxicity), such as seizures, tremors, or headache; and elevated potassium levels (hyperkalemia). However, FDA is not aware of post-marketing issues regarding safety or efficacy for Accord Healthcare Inc.'s tacrolimus oral capsules.

As a result of its review of this new information, FDA has changed the therapeutic equivalence rating for Accord Healthcare Inc.'s tacrolimus oral capsules from AB to BX. A BX rating means that the data are insufficient to show that Accord Healthcare Inc.'s tacrolimus oral capsules provide the same therapeutic effect as Prograf (tacrolimus) oral capsules. This means that Accord Healthcare Inc.'s tacrolimus oral capsules are still FDA-approved and can be prescribed, but are no longer recommended as automatically substitutable at the pharmacy (or by a pharmacist) for Prograf (tacrolimus) oral capsules.

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Prograf (tacrolimus) oral capsules and generic tacrolimus oral capsules manufactured by companies other than Accord Healthcare Inc. are not affected by this issue. Other tacrolimus dosage forms are also not affected by this issue, including tacrolimus extended-release oral capsules, tacrolimus granules for oral suspension, tacrolimus injection products for intravenous use, and tacrolimus topical ointments.

Patients can determine the manufacturer of their tacrolimus oral capsules by contacting their pharmacy. Patients currently taking Accord Healthcare Inc.'s tacrolimus oral capsules should not make changes to their treatment, except in consultation with their health care professional. Patients should also inform their health care professional if they have experienced any problems that may be related to taking Accord Healthcare Inc.'s tacrolimus oral capsules.

FDA encourages health care professionals and consumers to report adverse events or quality problems with these or any medications to FDA's MedWatch Adverse Event Reporting program:

- Complete and submit the report **online**; or
- Download and complete the **form**, then submit it via fax at **1-800-FDA-0178.**

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