CERTARA®

Accelerating Medicines, Together

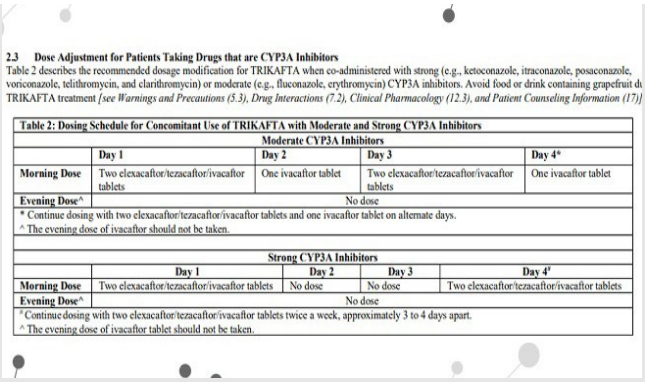
CASE STUDY

To View Online: certara.com/case-study/strategic-planning-and-technology-to-support-a-rolling-bla-submission-under-tight-timelines/

DETERMINING EXPOSURES WHEN TRANSITIONING BETWEEN COMBINATION TREATMENTS IN CYSTIC FIBROSIS: TRIKAFTA

Many cystic fibrosis (CF) patients take several medications at one time to manage symptoms and the disease. In 2012, FDA approved Ivacaftor (Kalydeco®) for treatment of the underlying cause of CF in a small subset of the patient population. In 2015, a combination treatment of Ivacaftor and Lumacaftor (Orkambi®), followed by a combination of Ivacaftor and Texacaftor (Symdeko®) in 2018. In 2019, the first triple combination of Elexacaftor/Texacaftor/Ivacaftor (Trikafta®) for patients 12 and up, accounting for about 90% of patients with CF was approved.

Many CF patients that take modulator regimens of the above dual combinations will need to transition to the triple combination. An assessment of whether adequate exposures to achieve clinical efficacy are maintained during this transition was needed, as this has not been directly addressed in clinical trials. PBPK modeling using Simcyp was used for this analysis, specifically to understand the CYP3A4 interactions during the CF transmembrane conductance regulator (CFTR) process. Individual models for each drug were developed, followed by simulations of various combination to assess exposure.



2.3 Dose Adjustment for Patients Taking Drugs that are CYP3A Inhibitors

Table 2 describes the recommended dosage modification for TRIKAFTA when co-administered with strong (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin) or moderate (e.g., fluconazole, erythromycin) CYP3A inhibitors. Avoid food or drink containing grapefruit d TRIKAFTA treatment *(see Warnings and Precautions (5.3), Drug Interactions (7.2), Clinical Pharmacology (12.3), and Patient Counseling Information (17))*

Table 2: Dosing Schedule for Concomitant Use of TRIKAFTA with Moderate and Strong CYP3A Inhibitors

	Moderate CYP3A Inhibitors			
	Day 1	Day 2	Day 3	Day 4*
Morning Dose	Two elexacaftor/tezacaftor/ivacaftor tablets	One ivacaftor tablet	Two elexacaftor/tezacaftor/ivacaftor tablets	One ivacaftor tablet
Evening Dose^	No dose			

* Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets and one ivacaftor tablet on alternate days.
^ The evening dose of ivacaftor should not be taken.

	Strong CYP3A Inhibitors			
	Day 1	Day 2	Day 3	Day 4*
Morning Dose	Two elexacaftor/tezacaftor/ivacaftor tablets	No dose	No dose	Two elexacaftor/tezacaftor/ivacaftor tablets
Evening Dose^	No dose			

* Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart.
^ The evening dose of ivacaftor tablet should not be taken.

The PBPK modeling demonstrated that immediate transfer from the three dual combinations to the triple combination resulted in sustained CFTR in patients 12 years and higher. Clinical trials on younger patients are ongoing.

> "Today's landmark approval is a testament to these efforts, making a novel treatment available to most cystic fibrosis patients, including adolescents, who previously had no options and giving others in the cystic fibrosis community access to an additional effective therapy."
>
> **Ned Sharpless, M.D.**
> Acting FDA Commissioner

Source: FDA Press release (https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis)

CF is an inherited condition that causes sticky mucus to build up in the lungs and digestive system. This causes lung infections and problems with digesting food. Symptoms usually start in early childhood and vary from child to child, but the condition gets slowly worse over time, with the lungs and digestive system becoming increasingly damaged.

CONTACT US TO LEARN MORE

HTTPS://WWW.CERTARA.COM/COMPANY/CONTACT/