International Journal of Basic & Clinical Pharmacology
Ahmud MW et al. Int J Basic Clin Pharmacol. 2025 Jul;14(4):649-650
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20251852

Letter to the Editor

A rare disease gets a breakthrough: Ctexli approved for cerebrotendinous xanthomatosis

Sir,

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive lipid storage disorder caused by mutations in the CYP27A1 gene, leading to sterol 27-hydroxylase deficiency and cholestanol accumulation. Ctexli's features range from infantile diarrhea to adult-onset neurodegeneration. Early diagnosis and treatment with chenodeoxycholic acid (CDCA) can significantly improve outcomes. Recently, the FDA approved Ctexli (chenodiol), a synthetic form of CDCA, as the first standardized treatment for CTX. Clinical trials demonstrated its efficacy in reducing plasma cholestanol and urinary bile alcohols. Ctexli's approval represents a significant advancement, enabling more consistent therapy and highlighting the importance of early intervention in managing CTX.

CTX, also referred to as cerebral cholesterolosis, is a rare autosomal dominant disease that affects one in every million people worldwide, with a higher frequency in the Moroccan Jewish population (1 among 108 people).[1] This condition is caused by a mutation in the CYP27A1 gene, leading to sterol 27-hydroxylase deficiency. Anyone without this enzyme cannot convert cholesterol into CDCA, a bile acid. As a result, the cholesterol levels are elevated and then transformed into cholestanol. Cholestanol has a predilection to accumulate in the organ systems of the body, notably in the central nervous system (CNS), eyes, arteries, and tendons, leading to the hallmark findings of diarrhea in an infant, juvenile-onset cataract, tendon xanthomas, and adult-onset progressive neurodegenerative disorder.[2]

As the symptoms vary from person to person, further gene testing (CYP27A1) and neuroradiologic testing are required.[2] Although CTX is very treatable, an early diagnosis and initiation of medical therapy improve patient outcomes. CDCA is the main and most effective treatment for CTX, which lowers cholestanol levels, thus improving symptoms. CDCA is most efficacious when started early and is generally safe. Other alternatives like cholic acid, statins, clofibrate, cholestyramine, and low-density lipoprotein apheresis show minimal benefit. Initiation of CDCA therapy requires regular follow-ups and treatment adherence to prevent disease progression.[3]

The Food and Drug Administration (FDA) recently approved Ctexli (chenodiol), a synthetic form of the bile acid CDCA, as the first FDA-approved drug to treat CTX. Ctexli works to replace the inadequate levels of CDCA, which reduces the abnormal deposition of cholesterol metabolites (cholestenol) responsible for the clinical presentation of CTX.[4] The efficacy of Ctexli against CTX was assessed through a double-blind, placebo-controlled, crossover trial, which showed that patients treated with Ctexli showed a significant reduction in plasma cholesterol metabolites (cholestanol and urine 23S-pentol) compared to patients treated with placebo.

The recommended dosage is 250 milligrams orally, three times daily. Ctexli is associated with common adverse reactions that include diarrhoea, headaches, abdominal pain, constipation, hypertension, and muscular weakness. Due to the liver toxicity risk of Ctexli, it's important to check liver enzymes - alanine aminotransferase, aspartate aminotransferase, and total bilirubin - before starting and annually while on treatment to ensure liver function is within a safe range. Signs of liver toxicity during treatment require seeking medical attention and discontinuation of the drug.[4]

Previously, CDCA, a naturally occurring bile acid that has been the primary treatment for CTX, showed a statistically significant reduction in blood cholestanol and urinary bile alcohols through multiple clinical studies over 5 to 10 years. In a literature review, biochemical outcomes improved in all participants, while clinical outcomes improved in 70% of them.[5]

However, Ctexli's approval brings a standardized and quality-controlled treatment; this synthetic version allows it to meet modern pharmaceutical standards. Being FDA approved, it can now be prescribed confidentially, boosting its accessibility, affordability, and fidelity.

As the newly FDA-approved drug enters the market, Ctexli represents a notable advancement in the treatment of CTX. Its approval calls attention towards earlier, more effective intervention in this rare and serious health condition.

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Cite this article as: Ahmud MW, Mustafa M, Asim W. A rare disease gets a breakthrough: Ctexli approved for cerebrotendinous xanthomatosis. Int J Basic Clin Pharmacol 2025;14:649-50.