

Triheptanoin and Glut1 Deficiency

Frequently Asked Questions

This document was compiled, authored and edited by the Glut1 Deficiency Foundation, with cooperation and support from Matthew's Friends. We acknowledge with gratitude the assistance and insights of numerous experts committed to improving the lives of Glut1 Deficiency patients and families.

This FAQ has been prepared and shared with the intent to help answer questions for those interested in triheptanoin as it relates to Glut1 Deficiency and with hopes that it will give families information to help make decisions about what is in the best interests of their Glut1 Deficiency patients.



TRihePTANOIN (C7 OIL) and GLUT1 DEFICIENCY FAQ

What is triheptanoin?

Triheptanoin, sometimes called “C7 Oil,” is a triglyceride oil (a fat) that is composed of three seven-carbon fatty acids. It is synthesized by a process of esterification of glycerol with heptanoic acid, each of which is easily derived from common natural oils. Triheptanoin is almost flavorless and colorless. It is used as an ingredient of cosmetic products and is added to butter in some European countries to allow for the tracing of the origin of the butter. Administration of triheptanoin as a dietary supplement is currently under investigation as a therapy for Glut1 Deficiency. Triheptanoin is also used experimentally to treat a variety of metabolic disorders such as Fatty Acid Oxidation Disorder (FAOD), Pyruvate Carboxylase Deficiency and Carnitine Palmitoyltransferase II Deficiency, and is under investigation as a potential therapy for epilepsy and Alzheimer’s disease.

Why is triheptanoin being investigated?

In patients with Glut1 Deficiency, glucose, which is normally the primary source of energy for the brain, is not transferred across the blood-brain barrier in sufficient quantities, leaving the brain starved for energy. When ingested, triheptanoin is converted into ketone bodies in the liver, which are able to cross the blood-brain barrier and provide an alternative source of energy for the brain. The process by which this occurs is through the conversion of the ketone bodies into acetyl-coenzyme A (acetyl-CoA), the principal fuel of the tricarboxylic acid cycle (the “TCA,” “Citric Acid” or “Krebs” cycle). The TCA cycle is the chemical process that produces energy, in the form of ATP, for use by the cells of the brain. However, in a brain with a glucose deficit, the TCA cycle may not be fully functional, even when fueled by acetyl-CoA derived from ketone bodies, due to inadequate concentrations of intermediate substrate compounds otherwise present in normal metabolic function. In this respect Triheptanoin is also thought to have an anaplerotic role. Anaplerosis refers to an enzyme catalyzed reaction that can replenish the supply of intermediates in the TCA cycle. Triheptanoin fulfills an anaplerotic function by providing pyruvate for carboxylation into oxaloacetate, a key intermediate substrate of the TCA cycle.

How is triheptanoin therapy thought to be different from the ketogenic diet?

The two principal metabolic roles of glucose are (1) energy production by oxidation of acetyl-CoA and (2) anaplerosis, by providing pyruvate (through the process of glycolysis) for carboxylation into oxaloacetate, an intermediate substrate of the TCA cycle. In a patient with Glut1 Deficiency, both of these roles may be impaired in the brain as a result of the deficit of glucose. The ketogenic diet causes the body to generate ketones from common dietary fat. These ketones are able to cross the blood brain barrier and provide an alternative source of energy for the brain in the form of acetyl-CoA, fulfilling the first metabolic role. However, the ketones produced as a result of the ketogenic diet are even-carbon ketones. Even-carbon ketones provide the brain with energy, but are not anaplerotic. Since triheptanoin is composed of odd-carbon fatty acids, it can produce ketone bodies with five carbon atoms as well as ketone bodies with four carbon atoms. The even-carbon fatty acids in common dietary fat are metabolized only into ketone bodies with four carbon atoms. The five-carbon ketones produced from triheptanoin are beta-ketopentanoate and beta-hydroxypentanoate. Each of these ketone bodies easily crosses the blood-brain barrier. The odd-carbon ketones produced from triheptanoin are thought to be anaplerotic in addition to providing the brain with an alternative source of energy, thus fulfilling both of the principal metabolic roles of glucose.

Has triheptanoin been proven to be an effective therapy for Glut1 Deficiency?

Not yet. Dr. Juan Pascual's team at the Rare Brain Disorders Clinic and Laboratory, Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center in Dallas has examined the metabolism of triheptanoin in the brains of Glut1 deficient mice and normal mice.¹ These studies were prompted by collaboration between Dr. Pascual and Dr. Charles Roe, who has for many years studied the mechanism of triheptanoin metabolism in the context of fatty acid oxidation disorder (FAOD). The studies found that triheptanoin produces significantly higher levels of acetyl-CoA in the brains of Glut1 deficient mice as compared to normal mice (suggesting its oxidation as an alternative energy source for the brain). The studies also found an increase of plasma glucose in both Glut1 deficient and normal mice, confirming that triheptanoin was being transformed into pyruvate, enabling gluconeogenesis to take place.

¹ [Heptanoate as a neural fuel: energetic and neurotransmitter precursors in normal and glucose transporter I-deficient \(G1D\) brain.](#) Marin-Valencia I, Good LB, Ma Q, Malloy CR, Pascual JM **J Cereb Blood Flow Metab** 2013 Feb;33(2):175-182. doi: 10.1038/jcbfm.2012.151. Epub 2012 Oct 17.

Based on encouraging results from the mouse studies, Dr. Pascual's team initiated a pilot study of the effects of ingestion of triheptanoin as a dietary supplement on human patients with Glut1 Deficiency in the summer of 2012. Patients enrolled in the trial were not on the ketogenic diet, and were observed before and immediately after ingesting triheptanoin, as well as after three months of triheptanoin therapy, and in some cases three months following termination of triheptanoin therapy. Principal observations were by electroencephalogram (EEG), specialized magnetic resonance imaging (MRI) and neuropsychological examination. The trial concluded in early 2013. Preliminary results of this trial presented by Dr. Pascual's team at the Curing the Epilepsies 2013 conference sponsored by the National Institute of Neurological Disorders and Stroke at the National Institutes of Health indicate that Glut1 Deficiency patients receiving triheptanoin can experience increased oxygen cerebral metabolic rate (CMRO2) by MRI, decreased seizures by EEG, and improved neuropsychological performance.² The final results of the trial are expected to be published within the coming months.

At the July, 2013 conference in Houston sponsored by the Glut1 Deficiency Foundation, Dr. Pascual adopted a cautionary note in regard to triheptanoin as a mature therapy for Glut1 Deficiency. He emphasized that triheptanoin is just one research option, and that it would be premature to think that it is the solution to Glut1 Deficiency without further solid laboratory research, as Glut1 Deficiency is not a well-understood disorder. Dr. Pascual maintained that better treatments will come from more and better laboratory research. He stated that his is presently the only lab and clinic using triheptanoin in Glut1 Deficiency, and indicated that while he is pleased to be well ahead in understanding how triheptanoin works and how human research on triheptanoin and related options should be conducted, we should be under no illusion that triheptanoin is ready for broad testing or use³.

² Synopsis of poster presentation #42 – **Synaptic Excitation–Inhibition Imbalance in Neuroglycopenia and Treatment of Its Associated Human Epilepsy With Triheptanoin**, J.M. Pascual, L. Good, P. Liu, I. Marin–Valencia, Q. Ma, M. Tondo, J. Park, D. Kelly, A. Hernandez, P. Stavinoha, C. Malloy, H. Lu. University of Texas Southwestern Medical Center, Dallas, TX. (https://meetings.ninds.nih.gov/assets/2013epilepsies/CuringEpilepsies2013_PROGRAMBOOK.pdf), page 42.

³ 2013 Glut1 Deficiency Foundation Conference Summary Report (<http://www.g1dfoundation.org/wp-content/uploads/2013/08/2013-Conference-Summary.pdf>)

Has triheptanoin been proven to be safe?

Triheptanoin has been shown to be safe when ingested by humans in amounts up to the equivalent of a significant percentage of the body's total daily caloric intake requirements through data gathered over a period of over twenty years. Side effects of larger doses have been observed in some cases to include stomach upset and/or diarrhea. These side effects can often be ameliorated by mixing with other foods and extending the time period of ingestion. Like other oils, triheptanoin can be mixed easily with low-fat, low-sugar yogurt, ice cream, pudding or other meals.

How can I obtain triheptanoin for my child with Glut1 Deficiency?

At the present time, triheptanoin can only be used as a dietary supplement in the U.S. by individuals enrolled in medical research studies of metabolic disorders regulated by the U.S. Food and Drug Administration (FDA), and can only be obtained and used under the supervision of authorized researchers. Some of the participants in the 2012 clinical trial conducted by Dr. Pascual's team requested to continue to use triheptanoin as a dietary supplement under the supervision of Dr. Pascual. These participants continue to receive triheptanoin directly from Dr. Pascual.

Can triheptanoin be administered in conjunction with the ketogenic diet?

Although there has been some speculation that triheptanoin taken in conjunction with the ketogenic diet might be more effective than either therapy administered alone, this has not been tested. It is thought that triheptanoin might be incompatible with some components of the ketogenic diet, such as MCT Oil. In addition, indications of the presence of gluconeogenesis in the mouse studies conducted by Dr. Pascual's team suggest the possibility that ingestion of triheptanoin could result in glucose production that would inhibit the ability of the ketogenic diet to maintain required ketone levels in the body. The conditions of compatibility of triheptanoin with the ketogenic diet are of interest to Dr. Pascual's team and may form the basis for a future clinical trial.

Are there any other clinical trials of triheptanoin available in which I could enroll my Glut1 Deficiency patient?

Not at present. However additional clinical trials involving triheptanoin are in the planning stages by Dr. Pascual's laboratory as well as other cooperating research laboratories worldwide. In addition, a private company, Ultragenyx Pharmaceuticals Inc., has announced plans to initiate a global phase 2 study of the safety and efficacy of their own highly purified form of triheptanoin to treat Glut1 Deficiency.⁴

Who is Ultragenyx Pharmaceuticals and why are they planning to initiate a clinical trial of triheptanoin?

Ultragenyx Pharmaceuticals describes itself as “a privately held, clinical-stage biotechnology company committed to bringing to market life-transforming therapeutics for patients with rare and ultra-rare metabolic genetic diseases.”⁵ Ultragenyx became involved with triheptanoin in early 2013, when it licensed rights to triheptanoin from Baylor Research Institute.⁶ In the spring of 2013, Ultragenyx contacted the Glut1 Deficiency Foundation and communicated its interest in investigating triheptanoin as a candidate treatment for Glut1 Deficiency. A letter from Ultragenyx describing its interest in Glut1 Deficiency was published in the Spring 2013 newsletter of the Glut1 Deficiency Foundation.⁷ Ultragenyx plans to test a “highly purified form of triheptanoin, which is produced using a GMP-compliant process required to obtain drug approval from the FDA and other regulatory agencies.”⁸ UX007 is Ultragenyx' product name for this material.

⁴ Ultragenyx Pharmaceuticals press release of August 5, 2013 (<http://www.ultragenyx.com/index.php?ht=action/GetDocumentAction/i/13712>)

⁵ Ultragenyx Pharmaceuticals press release of July 11, 2013 (<http://www.ultragenyx.com/index.php?ht=action/GetDocumentAction/i/13018>)

⁶ Ultragenyx Pharmaceuticals press release of January 10, 2013 (<http://www.ultragenyx.com/index.php?ht=action/GetDocumentAction/i/8705>)

⁷ Glut1 Deficiency Foundation, Spring 2013 Newsletter (<http://www.g1dfoundation.org/wp-content/uploads/2013/05/Spring-2013-G1D-News.pdf>)

⁸ Ultragenyx Pharmaceuticals press release of August 5, 2013 (<http://www.ultragenyx.com/index.php?ht=action/GetDocumentAction/i/13712>)

What is the difference between UX007 and the triheptanoin that is already under investigation at other sites?

To date, most all investigators, including Drs. Pascual and Roe, have used what is considered by the FDA and manufacturers to be “food grade” triheptanoin. The safety record for ingestion of food grade triheptanoin extends over a period of over twenty years, and its effectiveness as a potential therapy for Glut1 Deficiency has been the subject of mouse studies followed by the human clinical trial conducted by Dr. Pascual’s team in 2012. Ultragenyx subjects triheptanoin to additional purification “which is intended to reduce taste and odor with the goal of enhancing patient compliance”⁹ and to produce what it considers to be a pharmaceutical grade of triheptanoin (UX007) in order to seek approval from the FDA to market UX007 as a drug.¹⁰

Will triheptanoin ever become available for my child with Glut1 Deficiency without participation in a clinical trial?

There are several possible regulatory avenues by which triheptanoin may in the future gain approval for distribution for the purpose of human consumption in the US.

DRUG

One avenue, which Ultragenyx has stated that it intends to pursue, is to petition the FDA for approval of triheptanoin (or Ultragenyx’ UX007) as a prescription drug. If approved as a drug, triheptanoin would become available to purchase from a pharmaceutical company based on a prescription from your physician. As a prescription drug, triheptanoin might also be eligible for insurance reimbursement, depending on the terms of your insurance policy.

The process for obtaining approval of a new drug is typically lengthy and very expensive, and a new drug approval can therefore be a valuable asset for a pharmaceutical company. It has been reported that it takes on average 12 years and over 350 million dollars to gain FDA approval for a new drug.¹¹ A typical approval process would involve three phases of clinical trials.¹²

⁹ Ultragenyx Pharmaceuticals press release of July 11, 2013 (<http://www.ultragenyx.com/index.php?ht=action/GetDocumentAction/i/13018>)

¹⁰ Ultragenyx Pharmaceuticals press release of August 5, 2013 (<http://www.ultragenyx.com/index.php?ht=action/GetDocumentAction/i/13712>)

¹¹ Drugs.com, New Drug Approval Process (<http://www.drugs.com/fda-approval-process.html>)

¹² See FDA Drug Review Process (<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm289601.htm>); See also FDA, Inside Clinical Trials: Testing Medical Products in People (<http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143531.htm>)

Phase 1 trials usually involve healthy volunteers and are conducted to gain information on how the body metabolizes a proposed drug, dosing and any serious side effects.

Phase 2 trials normally involve 100 to 300 volunteers who have the condition the proposed drug is intended to treat. The purpose of phase 2 trials is usually to develop further information on safety and to begin to determine the efficacy of the proposed drug.

Phase 3 trials typically study the effect of the drug in a larger number of patients having the target condition (approximately 1,000 to 3,000), and are designed to further test safety and efficacy, and sometimes to compare the effectiveness of the proposed drug with the standard treatment for the target condition, if one exists.

Phase 2 and 3 trials are often conducted on a double blind basis and usually require the use of control groups who either receive the standard treatment, a placebo or both, a decision dependent on ethical considerations where withholding treatment would involve unacceptable risks for patients. In the case of drugs to treat rare diseases such as Glut1 Deficiency there is sometimes relief available from the more strict regulatory requirements applicable to treatments for more common conditions through an orphan drug designation under the Orphan Drug Act. Safety and effectiveness of an orphan drug must still be established through adequate and well-controlled studies, but smaller trials may be approved in recognition of the fact that only a small number of people have been identified with the target condition. The sponsor of an orphan drug in the U.S. can obtain an exclusive seven year right to market the drug and may be eligible for tax incentives.

To learn more about clinical trials and important points to consider, please visit the [Learn About Clinical Trials](#) section at [Clinical Trials.gov](#), a service of the United States National Institutes of Health.

MEDICAL FOOD

Another possible avenue for distribution of triheptanoin might be as a “medical food.”¹³ A medical food is defined in the Orphan Drug Act as “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.” Medical foods are not regulated as drugs and are exempt from any premarket review and approval by the FDA. They are furthermore exempt from certain labeling requirements for health

¹³ See FDA, Draft Guidance for Industry: Frequently Asked Questions About Medical Foods; Second Edition (<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/ucm054048.htm>); See also FDA, Medical Foods Compliance Program, Import and Domestic (<http://www.fda.gov/downloads/Food/ComplianceEnforcement/UCM073339.pdf>)

claims and nutrient content claims, although they must comply with general labeling requirements applicable to foods. Medical foods must comply with all other FDA requirements for foods, including the Current Good Manufacturing Practice regulations and Registration of Food Facilities regulations. Although a medical food does not require a prescription, the FDA takes the position that “the intended use of a medical food is for the dietary management of a patient receiving active and ongoing medical supervision (e.g., in a health care facility or as an outpatient) of a physician who has determined that the medical food is necessary to the patient's overall medical care. The patient should generally see the physician on a recurring basis for, among other things, instructions on the use of the medical food.” Medical foods moreover are explicitly approved by the FDA for the treatment of “inborn errors of metabolism.” Inborn errors of metabolism are genetic diseases involving disorders of metabolism. Glut1 Deficiency is considered an inborn error of metabolism of the Glucose Transporter Type 1, and would appear to be a logical candidate for treatment with triheptanoin under the FDA’s medical food regime.

DIETARY SUPPLEMENT

A third possible avenue for distribution of triheptanoin in the future could be as a dietary supplement (however, it would not be possible to market a dietary supplement as a treatment or cure for a specific condition such as Glut1 Deficiency, as marketing as a treatment or cure is reserved for drugs and medical foods).¹⁴ Dietary supplements occupy a special legal category under the general umbrella of “foods” rather than “drugs.” By law, the manufacturer and distributor of a dietary supplement is responsible for determining that the dietary supplements it manufactures or distributes are safe, and any marketing claims made by the manufacturer or distributor would need to be substantiated by adequate evidence to show that they are not false or misleading. Where the supplement, or an ingredient, was not marketed in the U.S. prior to October 15, 1994, a pre-market review by the FDA of safety data and other information is required. Except for the pre-market review of safety data in the case of a new dietary ingredient, dietary supplements do not need approval from FDA before they are marketed. As in the case of medical foods, the FDA has adopted regulations defining Current Good Manufacturing Practices for those who manufacture, package or hold dietary supplements.

Approval as a drug or distribution as a medical food or as a dietary supplement are possible avenues by which triheptanoin may become more generally available in the future. Others may exist as well. It is important that members of the Glut1 Deficiency community continue to monitor the activities of individuals and organizations seeking to bring to market new treatments or therapies for Glut1 Deficiency and make their views and preferences known directly and through available legislative and regulatory channels.

¹⁴ See FDA, QA on Dietary Supplements (http://www.fda.gov/Food/DietarySupplements/QADietarySupplements/#FDA_role)

Why should I care how triheptanoin might be approved as long as it becomes available for me to try with my Glut1 Deficiency child?

Different pathways to approval of triheptanoin for human consumption in the U.S. may result in very different conditions of availability. For example, a drug, newly approved after a long and costly approval process, will likely be very expensive, in order that the pharmaceutical company can recover its costs and make a profit. However, it will have successfully completed FDA approved trials for safety and efficacy as a treatment specifically for Glut1 Deficiency, and the high cost might be covered by your insurance company, depending on the terms of your policy. Unless triheptanoin is shown in future trials to be more effective than the ketogenic diet, there may remain a question as to the willingness of insurance companies to reimburse the cost of triheptanoin as a drug where the ketogenic diet is available as a less expensive alternative.

Marketed as a medical food or dietary supplement, triheptanoin would likely be significantly less expensive. However, a medical food or dietary supplement might not be reimbursed by your insurance company, and it would not be required to undergo the same clinical testing process as a drug.

What is the position of the Glut1 Deficiency Foundation on triheptanoin and other experimental treatments for Glut1 Deficiency?

The Glut1 Deficiency Foundation is committed to our mission of supporting researchers as they work for better treatments and an ultimate cure. It is the position of the Foundation's Board of Directors that continued basic laboratory research into triheptanoin therapy and other experimental treatments for Glut1 Deficiency serves the best interests of all in the Glut1 Deficiency community. Several investigators have been at the forefront of laboratory research in this area for many years, and the Foundation has been supportive of these efforts since its beginning. The commitment of cooperating research laboratories worldwide to thorough investigation of the metabolic processes affected by Glut1 Deficiency and the mechanisms by which triheptanoin and other experimental therapies may assist in the restoration of those processes will help ensure that any recommendation that may be made for the use of triheptanoin or other experimental therapies in the future will be backed by a high level of understanding and a deep desire to support the Glut1 Deficiency community.