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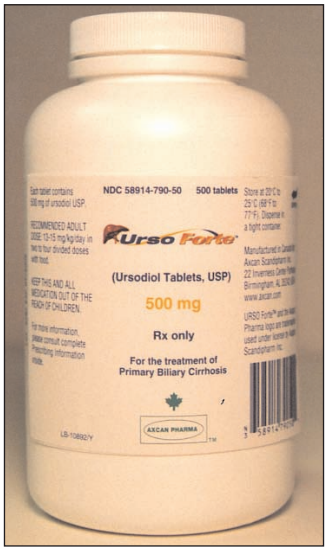
AXCAN PHARMA™ - DELIVERING THERAPIES THAT IMPROVE SURVIVAL AND ENHANCE THE QUALITY OF LIFE FOR PRIMARY BILIARY CIRRHOSIS

Axcan Pharma's (Mont Saint-Hilaire, Quebec) URSO Forte™ (500 mg ursodiol tablets, USP) and its lower dose equivalent, **URSO 250®,** (250 mg ursodiol tablets, USP) are the only FDA-approved ursodiol products for the treatment of Primary Biliary Cirrhosis (PBC). Since PBC cannot be cured, treatment is designed to slow the progression of the disease. Ursodiol has more than 10 years of clinical studies, proving effectiveness and safety and further showing that ursodiol tablets[1] reduce treatment failure and the need for liver transplant,[1,2] may slow down the progression of PBC, lengthening the time from diagnosis to the need for a liver transplant,[2,3] reduce the frequency of esophageal varices,[3,4] improve signs and symptoms of PBC with long-term treatment,[4] have few side effects, and are well tolerated by most patients.[1,3] The higher dose of URSO Forte™ may simplify treatment for patients with the convenience of taking fewer tablets per day, which can lead to better patient compliance. According to Kris V. Kowdley, MD, Professor of Medicine, University of Washington (Seattle, WA), "Given that there is a higher concentration of the active ingredient in the URSO Forte™ pill, the administration to the patient is vastly preferable. The other advantage of URSO Forte™ is the convenience of dosing. With the standard URSO 250® mg, the dosing was four times a day. Since ursodiol is best absorbed with a meal, this represents a complex challenge in terms of taking medications for a lot of patients. URSO Forte™ has been a significant advantage and improvement given that you have more flexible dosing options, which allows for more ease of administration."



The major issue from the standpoint of different ursodiol preparations is, are they exactly the same? The answer is no. URSO Forte™ and URSO 250® are the only ursodiol products available in a tablet formulation. Bile acid absorption fluctuates between different pharmaceutical preparations of UDCA and studies have shown that more of the active ingredient in ursodiol tablets is absorbed by the body when compared to ursodiol capsules.[5] One study involving 24 healthy subjects compared the bioavailability of four commercially available UDCA formulations in standard doses—two tablet preparations made separately in Canada and the USA (for the same company) and two capsule preparations, Actigall® and Ursolvan, made in Europe. The study demonstrated that the UDCA tablets had better absorption than the two UDCA capsule formulations.[5]

Melissa Palmer, MD, private practitioner, Hepatology and Gastroenterology (Plainview, NY), has extensive experience with URSO Forte™. "In my patient population, URSO Forte™ has few to no side effects, is easy to use and dose, and has excellent patient compliance and excellent results. The correct dosing in patients with cholestatic liver disease is extremely crucial. The beneficial effects of ursodeoxycholic acid are experienced by approximately 80 percent of people with PBC who use this medication, and these effects are most likely to occur the sooner a person is treated, i.e., when the person is treated during the first or second stage of the disease." Studies have shown that ursodiol tablets have been shown to benefit PBC patients by slowing histological progression and preventing death or transplantation when treatment is started in the early stages of the disease.[4] A study conducted by Jorgensen, *et al.*, confirmed this through evaluation of the outcome of UDCA treatment in 180 PBC patients over a 12-year period. Of the initial 89 patients originally assigned to UDCA treatment, there were 28 deaths and transplantations compared to 42 deaths and transplantations in the original placebo group of 91 patients, proving the benefit of UDCA.[4] Further, of the 70 total patients who died or required transplantation, 84% were in late histological stages (III and IV) at entry compared with 58% of living patients.[4]

Additionally, treatment with UDCA has been shown to increase survival in PBC patients without liver transplantation. A study by Poupon, *et al*., concluded that 10-year survival among UDCA treated patients is slightly lower than that of an age-and sex-matched general population, the difference explained in large part by death among cirrhotic patients.[6] E. Jenny Heathcote, MD, University of Toronto, Senior Scientist, Head-Clinical Studies Resource Centre, Toronto Western Research Institute (Toronto, Canada) says, "UDCA is not a cure, but it certainly appears to delay progression of disease and delay the progression of hepatic failure. The number of patients I need to send for liver transplant has markedly diminished."

Destruction of bile ducts leads to the retention of hydrophobic bile acids within the liver cell, and this most likely contributes to the gradual deterioration in liver function observed in patients with PBC.[7] Dr. Kowdley says that UDCA, by displacing toxic bile acids, "may have a cytoprotective effect on cell membranes and may also down-regulate the autoimmune response that might accelerate liver damage. UDCA is a hydrophilic bile acid and has a lot of favorable properties in that it can displace more toxic, or hydrophobic bile, acids that can accumulate within the liver in the setting of cholestatic liver disease. After oral administration of UDCA we achieve enrichment in the bile, and it has been suggested that you can get a 10-fold increase in biliary concentrations and the enrichment in the bile can go from about 4 percent to 40 or 50 percent. There are other data suggesting that UDCA, in addition to being a nontoxic bile acid, may promote bile flow, may make the bile less acidic and may make the bile more watery. So, it is attractive to speculate that all of these properties would work together in flushing toxic bile acids out of the liver and keeping bile ducts open and playing a role in healing and stopping progression of liver injury in cholestatic liver disease." Dr. Kowdley goes on to say, "There is data to support long-term use of UDCA in stopping the progression of fibrosis and although it's not entirely clear whether UDCA in PBC reverses advanced fibrosis, it is clear that the necroinflammatory changes, which are markers of cell damage, improve with ursodiol therapy."

The recommended adult dosage for URSO Forte™ in the treatment of PBC is 13-15 mg/kg/day administered in two divided doses with food. Dosing regimen should be adjusted according to each patient's need at the discretion of the physician.

Patients with variceal bleeding, hepatic encephalopathy, ascites or in need of an urgent liver transplant should receive appropriate specific treatment. To ensure efficacy, patients should delay taking aluminum-based antacids and bile-sequestering agents and should avoid estrogens, oral contraceptives, clofibrate (and possibly other lipid-lowering drugs). In clinical trials, the most common treatment emergent adverse events (<5%) were asthenia, dyspepsia, peripheral edema, hypertension, nausea, GI disorders, chest pain and pruritis. Contraindications include hypersensitivity or intolerance to ursodiol or any components of the formulation.

Axcan Pharma™ is a supporter of "The PBCers," an organized support system with more than 2,000 members worldwide, for patients, family and friends of those who suffer from PBC and other cholestatic liver diseases.

The physicians quoted in this piece have been involved in research activities with Axcan Pharma™.

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For more information about Axcan Pharma™, URSO Forte™, and URSO 250®, please call 1.800.472.2634. For full Prescribing Information visit the company's Web site at www.axcan.com, or contact a company representative at AASLD, booth #419.

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