

Actigall®
Ursodiol (Ursodeoxycholic acid)

Qualitative and quantitative composition

Actigall 300mg: Size 0 hard gelatin capsule with a pink cap and white body containing a white/yellowish powder branded in black "Actigall" on one part and "300mg" on the other.

Pharmaceutical form

Capsules for oral administration

Clinical particulars

Therapeutic indications

Chronic intrahepatic cholestatic diseases including primary biliary cirrhosis and primary sclerosing cholangitis.

In primary biliary cirrhosis Actigall improves liver enzymes and IgM and prevents worsening of liver histology in patients with less advanced forms of the disease, ie, serum bilirubin less than 2 mg/dL and histologic changes in liver confined to the portal regions. Prevention of complications of chronic liver disease has not been established.

Dosage and method of administration

For treatment of primary biliary cirrhosis(PBC) and primary sclerosing cholangitis (PSC), the recommended dose of Actigall is 10-12 mg/kg once-a-day. In patients taking bile acid binding resins for relief of pruritus, Actigall should be administered either 2-3 hours before or 4 hours after the doses of the resin.

Children

The safety and effectiveness of Actigall in children have not been established.

Geriatric Use

In worldwide clinical studies of Actigall, approximately 14% of subjects were over 65 years of age (approximately 3% were over 75 years old). In a subgroup analysis of existing clinical trials, patients greater than 56 years of age did not exhibit statistically significantly different complete dissolution rates from the younger population. No age-related differences in safety and effectiveness were found. Other reported clinical experience has not identified differences in response in elderly and younger patients. However, small differences in efficacy and greater sensitivity of some elderly individuals taking Actigall cannot be ruled out. Therefore, it is recommended that dosing proceed with caution in this population.

Contraindications

Actigall will not dissolve calcified cholesterol stones, radio-opaque stones or radiolucent bile pigment stones. Hence patients with such stones are not candidates for Actigall therapy.

Patients with compelling reasons for cholecystectomy including unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis or biliary-gastrointestinal fistula are not candidates for Actigall therapy.

Allergy to bile acids.

Special warnings and special precautions for use

Ursodiol therapy has not been associated with liver damage.

Lithocholic acid, a naturally occurring bile acid, is known to be a liver-toxic metabolite. This bile acid is formed in the gut from ursodiol less efficiently and in smaller amounts than that seen from chenodiol.

Lithocholic acid is detoxified in the liver by sulfation and although man appears to be an efficient sulfater, it is possible that some patients may have a congenital or acquired deficiency in sulfation, thereby predisposing them to lithocholate-induced liver damage.

Abnormalities in liver enzymes have not been associated with Actigall therapy and in fact Actigall has been shown to decrease liver enzyme levels in liver disease. However, patients given Actigall should have SGOT (AST) and SGPT (ALT) measured at the initiation of therapy and thereafter as indicated by the particular clinical circumstances.

Interaction with other medicinal products and other forms of interactions

Bile acid sequestering agents such as cholestyramine and colestipol may interfere with the action of Actigall by reducing its absorption. Aluminium-based antacids have been shown to adsorb bile acids in vitro and may be expected to interfere with Actigall in the same manner as the bile acid sequestering agents. Oestrogens, oral contraceptives and clofibrate (and perhaps other lipid-lowering agents) increase hepatic cholesterol secretion, and encourage cholesterol gallstone formation and hence may counteract the effectiveness of Actigall.

Pregnancy and lactation

There have been no adequate and well-controlled studies of the use of ursodiol in pregnant women, but inadvertent exposure of 4 women to therapeutic doses in the first trimester of pregnancy during the Actigall trials led to no evidence of effects on the foetus or newborn baby. Although it seems unlikely, the possibility that ursodiol can cause foetal harm cannot be ruled out; hence, Actigall is not recommended for use during pregnancy.

It is not known whether ursodiol is excreted in human milk. Because many substances are excreted in human milk, caution should be exercised when Actigall is administered to a nursing mother.

Effects on ability to drive and use machines

No data exist on the effects of Actigall on the ability to drive and use machines

Adverse effects

The following tables provide comprehensive listings of the adverse experiences reported that occurred with a 5% incidence level:

	GALLSTONE DISSOLUTION			
	Ursodiol 8-10 mg/kg/day (N=155)		Placebo (N=159)	
	N	(%)	N	(%)
Body as a Whole				
Allergy	8	(5.2)	7	(4.4)
Chest Pain	5	(3.2)	10	(6.3)
Fatigue	7	(4.5)	8	(5.0)
Infection Viral	30	(19.4)	41	(25.8)
Digestive System				
Abdominal Pain	67	(43.2)	70	(44.0)
Cholecystitis	8	(5.2)	7	(4.4)
Constipation	15	(9.7)	14	(8.8)
Diarrhoea	42	(27.1)	34	(21.4)
Dyspepsia	26	(16.8)	18	(11.3)
Flatulence	12	(7.7)	12	(7.5)
Gastrointestinal Disorder	6	(3.9)	8	(5.0)
Nausea	22	(14.2)	27	(17.0)
Vomiting	15	(9.7)	11	(6.9)
Musculoskeletal System				
Arthralgia	12	(7.7)	24	(15.1)
Arthritis	9	(5.8)	4	(2.5)
Back Pain	11	(7.1)	18	(11.3)
Myalgia	9	(5.8)	9	(5.7)
Nervous System				
Headache	28	(18.1)	34	(21.4)
Insomnia	3	(1.9)	8	(5.0)

GALLSTONE DISSOLUTION

	Ursodiol		Placebo	
	8-10 mg/kg/day			
	(N=155)		(N=159)	
	N	(%)	N	(%)

Respiratory System

Bronchitis	10	(6.5)	6	(3.8)
Coughing	11	(7.1)	7	(4.4)
Pharyngitis	13	(8.4)	5	(3.1)
Rhinitis	8	(5.2)	11	(6.9)
Sinusitis	17	(11.0)	18	(11.3)

Upper Respiratory

Tract Infection	24	(15.5)	21	(13.2)
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Urogenital System

Urinary Tract Infection	10	(6.5)	7	(4.4)
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GALLSTONE PREVENTION

	Actigall		Placebo	
	600 mg			
	(N=322)		(N=325)	
	N	(%)	N	(%)

Body as a Whole

Fatigue	25	(7.8)	33	(10.2)
Infection Viral	29	(9.0)	29	(8.9)
Influenza-like Symptoms	21	(6.5)	19	(5.8)

Digestive System

Abdominal Pain	20	(6.2)	39	(12.0)
Constipation	85	(26.4)	72	(22.2)
Diarrhea	81	(25.2)	68	(20.9)
Flatulence	15	(4.7)	24	(7.4)
Nausea	56	(17.4)	43	(13.2)
Vomiting	44	(13.7)	44	(13.5)

Musculoskeletal System

Back Pain	38	(11.8)	21	(6.5)
Musculoskeletal Pain	19	(5.9)	15	(4.6)

Nervous System

Dizziness	53	(16.5)	42	(12.9)
Headache	80	(24.8)	78	(24.0)

Respiratory System

Pharyngitis	10	(3.1)	19	(5.8)
Sinusitis	17	(5.3)	18	(5.5)

	GALLSTONE PREVENTION			
	Actigall 600 mg (N=322)		Placebo (N=325)	
	N	(%)	N	(%)
Upper Respiratory				
Tract Infection	40	(12.4)	35	(10.8)
Skin and Appendages				
Alopecia	17	(5.3)	8	(2.5)
Urogenital System				
Dysmenorrhea	18	(5.6)	19	(5.8)

Overdose

Neither accidental nor intentional overdosing with Actigall has been reported. Doses of Actigall in the range of 16-20 mg/kg/day have been tolerated for 6-37 months without symptoms by 7 patients. The LD₅₀ for ursodiol in rats is over 5000 mg/kg given over 7-10 days and over 7500 mg/kg for mice. The most likely manifestation of severe overdose with Actigall would probably be diarrhoea, which should be treated symptomatically.

Pharmacological properties

Pharmacodynamics properties

The precise mechanism of action of ursodiol in the treatment of primary biliary cirrhosis and primary sclerosing cholangitis remains uncertain, although its clinical benefits may result from several effects including: direct effects on the liver causing displacement of endogenous hydrophobic bile acids at hepatocyte and biliary epithelial membranes; competition at the site of ileal bile acid absorption; immunomodulation; and enhancement of choleresis.

Ursodiol suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol. It appears to have little inhibitory effect on synthesis and secretion into bile of endogenous bile acids, and does not appear to affect secretion of phospholipids into bile.

With repeated dosing, bile ursodeoxycholic acid concentrations reach a steady state in about 3 weeks. Although insoluble in aqueous media, cholesterol can be solubilized in at least two different ways in the presence of dihydroxy bile acids. In addition to solubilizing cholesterol in micelles, ursodiol acts by an apparently unique mechanism to cause dispersion of cholesterol as liquid crystals in aqueous media. Thus, even though administration of high doses (e.g., 15-18 mg/kg/day) does not result in a concentration of ursodiol higher than 60% of the total bile acid pool, ursodiol-rich bile effectively solubilizes cholesterol. The overall effect of ursodiol is to increase the concentration level at which saturation of cholesterol occurs.

After ursodiol dosing is stopped, the concentration of the bile acid in bile falls exponentially, declining to about 5%-10% of its steady-state level in about 1 week.

Pharmacokinetics

Absorption

About 90% of a therapeutic dose of Actigall is absorbed in the small bowel after oral administration. After absorption, ursodiol enters the portal vein and undergoes efficient extraction from portal blood by the liver (i.e. there is a large "first pass" effect) where it is conjugated with either glycine or taurine and is then secreted into the hepatic bile ducts. Ursodiol in bile is concentrated in the gallbladder and expelled into the duodenum in gallbladder bile via the cystic and common ducts by gallbladder contractions provoked by physiologic responses to eating. Only small quantities of ursodiol appear in the systemic circulation and very small amounts are excreted into urine. The sites of therapeutic action are in the liver, bile and gut lumen.

Beyond conjugation, ursodiol is not altered or catabolised appreciably by the liver or intestinal mucosa. A small proportion of orally administered ursodiol undergoes bacterial degradation with each cycle of enterohepatic circulation. Ursodiol can be both oxidised and reduced at the 7-carbon, yielding either 7-keto-lithocholic acid or lithocholic acid, respectively. Further, there is some bacterially catalysed deconjugation of glyco- and tauro-ursodeoxycholic acid in the small bowel. Free ursodiol, 7-keto-lithocholic acid and lithocholic acid are relatively insoluble in aqueous media and larger proportions of these compounds are lost from the distal gut into the faeces. Reabsorbed free ursodiol is reconstituted by the liver. Eighty percent of lithocholic acid formed in the small bowel is excreted in the faeces, but the 20% that is absorbed is sulfated at the 3-hydroxyl group in the liver to relatively insoluble lithocholyl conjugates which are excreted into bile and lost in faeces. Absorbed 7-keto-lithocholic acid is stereospecifically reduced in the liver to chenodiol.

Lithocholic acid is formed by 7-dehydroxylation of the dihydroxy bile acids (ursodiol and chenodiol) in the gut lumen. The 7-dehydroxylation reaction appears to be alpha-specific, i.e. chenodiol is more efficiently 7-dehydroxylated than ursodiol and for equimolar doses of ursodiol and chenodiol, levels of lithocholic acid appearing in bile are lower with the former. Lithocholic acid causes cholestatic liver injury and can cause death from liver failure in certain species unable to form sulfate conjugates. Man has the capacity to sulfate lithocholic acid. Although liver injury has not been associated with ursodiol therapy, a reduced capacity to sulfate may exist in some individuals, but such a deficiency has not yet been clearly demonstrated.

In bile-fistula rats, infused conjugates of ursodiol protect against cholestasis and hepatotoxicity induced by infusion of conjugated lithocholate, deoxycholate, chenodeoxycholate, and cholate. In vitro, ursodiol conjugates also protect against the damaging effects of toxic bile salts in systems using isolated human or rat hepatocytes, erythrocytes, or model membranes consisting of lecithin and cholesterol. These cytoprotective effects of ursodiol have been attributed to an inhibition of the solubilisation of cholesterol and phospholipid from cell membranes induced by the detergent effects of the other endogenous bile acids.

Preclinical safety data

Carcinogenicity

Ursodeoxycholic acid was tested in two-year oral carcinogenicity studies in CD-1 mice and Sprague-Dawley rats at daily doses of 50, 250 and 1000 mg/kg/day. It was not tumourigenic in mice. In the rat study, it produced statistically significant dose-related increased incidences of pheochromocytomas of adrenal medulla in males ($p=0.014$, Peto trend test) and females ($p=0.004$, Peto trend test). A 78 week rat study employing intrarectal instillation of lithocholic acid and tauro-deoxycholic acid, metabolites of ursodiol and chenodiol, has been conducted. These bile acids alone did not produce any tumours. A tumour-promoting effect of both metabolites was observed when they were co-administered with a carcinogenic agent. Results of epidemiologic studies suggest that bile acids might be involved in the pathogenesis of human colon cancer in patients who had undergone a cholecystectomy, but direct evidence is lacking. Ursodiol is not mutagenic in the Ames test. Dietary administration of lithocholic acid to chickens is reported to cause hepatic adenomatous hyperplasia.

Reproductive toxicity

Reproduction studies have been performed in rats and rabbits with ursodiol doses up to 200-fold the therapeutic dose and have revealed no evidence of impaired fertility or harm to the foetus at doses of 20 to 100-fold the human dose in rats and at 5-fold the human dose (highest dose tested) in rabbits. Studies employing 100 to 200-fold the human dose in rats have shown some reduction in fertility rate and litter size.

Pharmaceutical particulars

List of excipients

Maize Starch, colloidal silicon dioxide, magnesium stearate, black ink (opacode S-1R-8100HV), gelatin capsules.

Incompatibilities

None

Shelf life

3 years

Special precautions for storage

Store below 30°C . Dispense in a tight container (USP).

Nature and contents of the container

Actigall is supplied in 300mg capsules. Each pack of Actigall contains 100 Capsules

Instructions for use/handling

None

Further Information

Clinical Results: Primary Biliary Cirrhosis

A multicentre, double-blind, placebo-controlled 2 year treatment trial in 151 patients with histologically proven primary biliary cirrhosis was conducted in the U.S. Patients were stratified at entry on the basis of serum bilirubin levels and liver histology. In patients whose entry serum bilirubin was less than 2 mg/dL, Actigall prevented the further rise in serum bilirubin encountered in those receiving placebo. Elevated values for liver enzymes (alkaline phosphatase, GGT, AST, ALT) and IgM fell significantly in Actigall-treated patients but remained unchanged in those on placebo. The Mayo risk factor score (Mayo R) utilised as a prognostic marker in untreated PBC patients remained stable in those on Actigall but worsened in those receiving placebo. Actigall prevented worsening of periportal necrosis and fibrosis in those patients whose entry histology had not yet progressed to fibrosis extending between portal tracts, or to cirrhosis. Favourable effects of Actigall on pruritus were observed but were not statistically significant. In patients whose entry serum bilirubin was equal to or greater than 2 mg/dL (mean value 5.1 mg/dL), Actigall resulted in moderate improvement in values for liver enzymes and had no effect on the Mayo R score or on liver histology.

In a second, single-centre, double-blind, placebo-controlled trial in 19 PBC patients, Actigall treatment for 6 months produced a significant improvement in liver biochemistry. Indicators of cholestasis including AP, GGT, and total bilirubin were all significantly lowered, and indicators of inflammation, ALT, and AST were also significantly improved. These improvements reverted toward the elevated pretreatment levels after withdrawal of Actigall. There was a statistically significant improvement in the Mayo R factor scores of Actigall-treated patients. The predictive value of the improved Mayo R factor in Actigall-treated patients is unknown.

There is also considerable published data on the use of ursodiol in the treatment of primary biliary cirrhosis.

Medicine classification

Prescription Medicine.

Name and address

Novartis New Zealand Limited

Private Bag 65904

Mairangi Bay

Auckland 0754

Building G, 5 Orbit Drive

Rosedale

Auckland 0632

Telephone: 09 361 8100

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