Table 53 (Con't)

C. Effect on Development of Esophageal Varices in Patients Without Varices at Baseline				
Number (Proportion) of Patients Developing Varices	8/70 (11%)	20/69 (29%)	18%	0.003 [Log-rank] 0.004 [Wilcoxon]
Mean Days to Developing Varices	1704	1503	201 days	
II. Double-Blind Portion (2-year Cutoff)				
A. Effect on Treatment Failure (Protocol-Stipulated Definition)				
Number (Proportion) of Patients that Failed[b]	20/86 (23%)	40/86 (47%)	24%	<0.01 [Fisher's Exact]
Mean Days to Failure	804 [n=86]	641 [n=86]	163 days	0.0001 [Log-rank]
Mean Days to Treatment Failure Stratified by Bilirubin (mg/dl) at Baseline				
BIL ≤1.8	822 [n=65]	656 [n=63]	166 days	0.003 [Log-rank]
>1.8	737 [n=21]	613 [n=23]	124 days	0.01 [Log-rank] 0.06 [Wilcoxon]
Mean Days to Treatment Failure Stratified by Histologic Stage at Baseline				
Histologic Stage I, II	756 [n=29]	676 [n=23]	80 days	0.02 [Log-rank]
III, IV	805 [n=54]	625 [n=59]	180 days	0.0003 [Log-rank]
B. Effect on Hepatic Biochemical Markers				
[ ]=Within Normal Range or ULN	Change at Endpoint From Baseline			
Total BIL [0.1 - 1.1 mg/dl]	- 0.63	0.80	1.43 (mg/dl)	<0.0001 [Log-rank]
AP [98 - 251 U/l]	-708.38	14.67	723.05 (IU/l)	<0.0001 [Log-rank]
SGOT [12 - 31 U/l]	-36.20	25.51	61.71 (IU/l)	<0.0001 [Log-rank]
ALB [3.5 - 5 g/dl]	0.12	0.03	0.09 (g/dl)	N.S. [Log-rank]
PT [8.4 - 12 sec]	- 0.05	0.26	0.31 (sec)	<0.02 [Log-rank]
IgM (64 - 400)	-151.89	31.78	183.67	<0.0001 [Log-rank]

Table 53 (Con't)

IgA (60 - 300)	- 1.11	26.17	27.28	<0.05 [Log-rank] 0.06 [Wilcoxon]
IgG (700 - 1500)	-93.96	59.55	153.51	<0.05 [Log-rank]
γ-Globulin [0.7 - 1.7 g/dl]	- 0.03	0.14	0.17 g/dl	<0.05 [Log-rank]
Cholesterol [up to 253]	-62	1.7	63.7 mg/100 ml	0.0001 [Log-rank]
Mayo Risk Score	-0.3	0.3	0.6	0.0007 [Log-rank]

a) Cox Proportional Hazards Model after adjusting for the Mayo Risk Score
b) This endpoint was also statistically significant favoring UDCA over PL [therapeutic gain=10%, p=0.01 (Log-rank) and 0.03 (Wilcoxon)] when results were assessed using the revised definition of treatment failure (see Table 34).

Significant improvements on symptoms or histologic parameters were not seen in the Mayo Clinic trial. The published literature data reveals inconsistent results when the effect of UDCA on these variables is evaluated. A number of factors may account for these inconsistencies and these are assessed below, separately for pruritus and histopathologic parameters.

Pruritus is probably the most important sign among PBC patients. Reasons not to show differences in effects on this symptom in clinical trial include the number of patients studied (the study is not sized adequately; consequently, there is no power to show statistically significant differences) together with the types of patients included/excluded in the clinical trial (by chance some trials may include patients that are more prone to respond to pruritus than others). Two additional factors are the concomitant administration of antipruritic medications (i.e. use of choleretics or bile acid binding resin to treat itching may be confounding) and the method (scales) to evaluate this highly subjective, non-specific, vague and strongly influenced by PL effect. Pruritus symptoms may vary from trial to trial. It is not inconceivable that gender may play a role. To demonstrate consistent effects on pruritus in women, the main subjects in PBC, may be more difficult than in men. [By analogy, chemotherapy-induced N&V occurs at a higher incidence and with a higher severity in women than men. Also, females respond less readily and less consistently to antiemetic medications (such as 5-HT_3 receptor antagonists) than males]. Oral contraceptives can trigger pruritus in PBC.

As many other studies, the Mayo Clinic trial incorporated a static analog scale describing the intensity of itching for a defined period of time. But this customary approach does not account for the differential patient threshold of symptom recognition mentioned above. Rigorous analysis of the effect of UDCA on pruritus is therefore hindered by the intermittent occurrence and varying intensity of this highly subjective complaint. These considerations assume that, given the right clinical-experimental conditions, a positive effect with UDCA would be shown. But together with variable results it is important to consider the widely accepted concept that pruritus has poor prognostic value.

The lack of effect of UDCA on pruritus in both of the randomized/double-blind/PL-controlled trials, one critical the other supportive in this NDA, is in contrast to reports from the French (Poupon et al.) and Greek (S.J. Hadziyannis et al.) studies with UDCA in PBC. For instance, in the Greek study, pruritus was "effectively controlled" (ameliorated or abolished) in 83% of the patients in the first year of treatment with UDCA. At the end of the second year, pruritus was effectively controlled in 61% of the patients given UDCA but in only 24% of those in the untreated controlled group. From analysis of data from a double-blind multicenter trial of UDCA in symptomatic PBC by the Italian multicenter group for the study of UDCA in PBC, P.M. Battezzatti et al. [Hepatology 17:332-338 (1993)] reported a statistically significantly lower pruritus score during treatment than was found at entry in the UDCA and PL groups. In his review of the matter, R.A. Rubin et al. [Ann. Intern. Med. 121:207-218 (1994)] proposed that these findings probably reflect the natural history of pruritus in patients with PBC. However, in several unblinded trials, UDCA treatment was, in some patients, associated with a marked improvement in pruritus and a decreased need for cholestyramine [reviewed by R.A. Rubin et al., (locus cited) (1994)].

As previously mentioned, the mechanism of pruritus in PBC is poorly understood. It has been proposed that increased opioidergic neurotransmission/neuromodulation (tone) in the CNS contributes to the pruritus of cholestasis [E.A. Jones and N.V. Bergasa, Gut 38:644-645 (1996)]. It is also conceivable that altered serotoninergic neurotransmission may contribute to the pruritus of cholestasis since ondansetron, a $5\text{-}HT_3$ serotonin receptor antagonist, may ameliorate the pruritus of cholestasis.[49] These new findings suggest that, in PBC patients with pruritus, therapeutic modalities in addition to UDCA, may be needed to exert significant, consistent and long-lasting antipruritic effects. All in all, the data suggest that pruritus is due to several mechanisms.[50] Also, some investigators suspect that cholestyramine, which is an effective antipruritic medication in some PBC patients, must be trapping an [pruritus-associated] anion (acid) in the gut

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[49] [H. Schworer et al. A. Gastroenterol. 33:265-274 (1993); Pain 61:33-37 (1995)].

[50] The pathogenesis of pruritus is unknown. In the final analysis, pruritus may have both a topical (skin) as well as a CNS component. BAs probably play an important role. For example, Poupon et al. found a strong correlation between the severity of pruritus and the degree of elevation of serum BA concentrations. Patients with pruritus and cholestasis as a result of cholangiopathy always have elevated circulating BAs. In cirrhosis with surgical portacaval shunt, BAs are considerably elevated but pruritus is always absent. In the study by L. Schoenfield et al. BA concentration in cutaneous blister fluid of patients with pruritic hepatobiliary disease, were related to the intensity of the pruritus. Following the initial demonstration by J.R. Thornton and M.S. Losowsky [Br. Med. J. 297:1241 (1988)] of an increase in methionine enkephalin levels in PBC and a correlation between this increase with bilirubinemia, several authors [N.V. Bergasa and E.A. Jones, Semin. Liv. Dis. 13:519 (1993)] have proposed a central component for pruritus. M.R. Friedman et al. [Amer. J. Med. 70:1011 (1981)] had already suggested that there was no direct cause for BA retention for the pruritus in cholestasis. Also, according to C.N. Ghent [Amer. J. Gastroenterol. 82:117 (1987)] the pruritus in cholestasis is related to effects of bile salts in the liver, not the skin. In favor of the central origin, several groups of investigators have shown that opiate antagonists (naloxone and namelfer) modulate the perception of pruritus and induce an opiate withdrawal syndrome.

that is not a bile acid. This substance is increased or is synthesized as a consequence of cholestasis and the result of bile regurgitation into the bloodstream. In spite of all of these constraints and as pointed out by U. Leuschner [Scand. J. Gastroenterol. 29(Suppl. 204):40-46 (1994)], pruritus is the only symptom that can be clearly identified in PBC patients. In patients without pruritus there is (based on both the literature published and the NDA controlled clinical trials) no other symptom or sign that allows a correct assessment of an improvement of QOL. Intractable (refractory) or disabling pruritus, requiring plasmapheresis, may be reasons for liver transplantation referral.

Also difficult to assess is the effect of drugs on histological parameters. These showed no significant improvement in either the Mayo Clinic or the Canadian Multicenter trial. Just as per pruritus, the published literature data reveals marked inconsistent results with UDCA treatment. U. Leuschner [Scand. J. Gastroenterol. 29(Suppl 204):40-46 (1994)] reported that, in a total of 1004 patients in 11 controlled trials, a statistically significant improvement in liver histology was shown in only two of these studies; in three others there was a positive trend. In three, there was no improvement and in three more trials histology was not examined. Many factors may account for these inconsistencies. These factors include a sampling error [B. Portmann and RNM Macsween].[51] Characteristically, in PBC, the portal and ductal lesions are focal in character and patchy in distribution, so they may escape detection, particularly in small needle biopsy specimens. Another factor may be the size of the study; no significant improvements may be seen if the sample is "small". Although it is not yet clear how many patients are needed to show a statistical difference in histologic parameters, there is always the possibility of a Type II error. This would be due to the pronounced noise and lots of interference between and among groups being compared and perhaps (although there are some data to the contrary, see below), insufficient treatment time.

An additional important factor that may explain differences in results in histologic parameters is the system used to classify the biopsy data. The lesions of PBC are characterized by destruction of interlobular and septal bile ducts, accompanied or followed by progressive portal and periportal inflammation, fibrosis, and loss of hepatocytes, leading ultimately to the development of cirrhosis. The differences in response do not seem to be due to a small number of histologic features assessed [staging: number of assessed morphologic features] or to an insufficient grading [characterization of the degree of histologic alteration]. Used in the Mayo Clinic trial, the Ludwig system **classifies** the lesions as I=portal hepatitis, II=periportal hepatitis, III=septal lesions and IV=overt cirrhosis. These lesions are, in turn, **characterized** by I=portal inflammation without piece meal necrosis (PMN), II=portal and periportal inflammation with PMN but no evidence of bridging fibrosis or necrosis, III=fibrous septa or bridging necrosis and IV=cirrhosis (agreed definition). Therefore the Ludwig system, which combines fibrosis and necroinflammatory activity, would not allow assessment of these parameters independently. But these parameters (fibrosis vs necroinflammatory

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[51] Diseases of the intrahepatic bile ducts. In: Macsween, R.N.M. et al., editors, Pathology of the liver, 2nd edition: Churchill Livingstone pp. 424-453 (1987)

activity) were independently assessed in the Canadian Multicenter trial, which also showed lack of effect of UDCA on the progression of histological staging in the treated patients [although a couple of histologic parameters were improved].

It is to be noted that, based on what is known about its pharmacodynamic activities, UDCA is not expected to have an effect on liver fibrosis in PBC. But it is not known if a beneficial effect (on liver histology) may materialize upon long-term treatment. In the eleven controlled studies mentioned above, only the Poupon et al. trial [NEJM (1991) and (1994)], revealed a clear histologic improvement with UDCA. If long-term treatment (i.e. 6 to 10 years) is needed to see a consistent effect, insufficient treatment time may explain the indecisive results obtained in the two NDA trials reviewed here. In those literature-published results from studies in which specific histological criteria were examined, improvements in certain parameters such as hepatocellular ballooning, bile duct paucity, ductular proliferation, inflammatory cell infiltration, necrosis and cholestasis have been reported [the French, Canadian (Heathcote's) and the U.S. (Combes') trials].

An additional important reason for the inconsistent results in histologic parameters with UDCA in PBC is the fact that - as pointed out by M.M. Kaplan [Adv. Intern. Med. 32:359-378 (1987)] - in a single liver **all stages (I-IV)** can be present simultaneously.[52] A consequence of such a realization is that staging (any) is of only limited value since, as expected, biopsy specimens frequently contain variable lesions at different stages of development. To complicate matters further, there is no consensus on the meaning of some of the features of the lesions in PBC and this issue has been amply discussed in the excellent book by G. Klatskin and H.O. Conn.[53] These authors have expressed concerns about the Ludwig system (used in the Mayo Clinic trial). They have pointed out that in the Ludwig's system (used by the Mayo Clinic in PBC studies for many years), the presence or absence of ductal lesions and ductular proliferation is disregarded. The classification of lesions in this system is relatively simple and readily applicable in the assessment of needle biopsy specimens. However, according to Klatskin and Conn, no convincing evidence has been presented to establish that this classification correlates

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[52] If one postulates a confidence interval of 90%, then, per patient nine biopsies are required at one given time in order to obtain reliable histological results. Follow-up biopsies over a period of several years do not reduce this dilemma, since the histological picture changes with time and therefore at each examination nine biopsies would be necessary [U. Leuschner, Scand. J. Gastroenterol. 29(Suppl.204):40-46 (1994)].

[53] [Histopathology of the liver, volume 1, Oxford University Press, New York, Chapter 11: Primary liver cirrhosis pp 189 through 200 (1993)].

For example, the widely held view that the interlobular and septal ducts are the initial site of injury and that all other features of the lesions are secondary to the retention and regurgitation of bile is open to question. Portal inflammation, erosion of the limiting plates, portal and periportal fibrosis and intralobular collections of lymphocytes, proliferating Kupffer cells and granulomas may be encountered in the apparent absence of damaged ducts. Although the failure to detect such ducts may be due to inadequate sampling, the alternative possibly cannot be excluded that in PBC, the portal and parenchymal lesions are attributable to the same pathogenetic mechanisms responsible for duct injury.

with longevity, the only reliable criterion of how far the disease has advanced. In their book, Klatskin and Conn cite their own long-term study of patients with PBC. They found that the duration of survival varies inversely with the extent of fibrosis, the degree to which the limiting plates are eroded and the severity of cholestasis [J. Roll et al., NEJM 308:1-7 (1983)]. A pessimistic view on this matter is that it is unlikely that in stage III and especially IV PBC, in which bile ducts have been destroyed and cirrhosis has already developed, therapies such as UDCA can cause significant histologic improvement. If this is true, one may be asking too much of UDCA. Or is it that, by expecting consistent improvements in histologic parameters we wish UDCA would do even more of what it already does?

The reviewer concludes that although no improvement in histological parameters were demonstrated in the Mayo Clinic trial - which enrolled all comers - one cannot dismiss the possibility of an effect under different experimental conditions [i.e. higher doses of UDCA given for long-term periods]. But it is important to state that the staging used was useful for several important reasons. The stratification of patients on the basis of histologic stage resulted in a reasonable balanced distribution of the patients with early vs those with advanced disease randomized to either UDCA or PL. [Similar histologic disease characteristics before the experimental treatment are essential to draw sound conclusions. Also, clinical studies based on a homogenous groups of high risk patients (like the grade IV patients enrolled in the Mayo Clinic trial) are more powerful in detecting a difference in treatment efficacy]. This reasoning leads to the realization that the beneficial effects of UDCA on survival and/or probability of liver transplantation (or referral), treatment failure (both revised and protocol-stipulated definition) and development of esophageal varices were shown in all patients as a whole (regardless of the histologic stage). The significant effects on treatment failure were further demonstrated whether the patients had mild (BIL ≤1.8 mg/dl) or moderate/severe (BIL >1.8 mg/dl) biochemical abnormalities or whether they had early (stages I & II) or advanced (stages III & IV) disease on the basis of histological parameters. These results appear to justify the sponsor's request that UDCA be approved for the treatment of PBC, all stages.

XI. OVERALL SUMMARY OF SAFETY

The safety data summarized in this section of the MO review, originate from the following sources:

A. The two clinical trials, one pivotal the other supportive, in NDA 20-675
B. The published literature on PBC patients
C. The published literature on other indications, including gallstone dissolution.

In addition, under subsection D. the MO briefly addresses long-term administration of UDCA and carcinogenicity.

A. Safety Data from Adequate and Well-Controlled Trials in NDA 20-675

Safety data originating from these two trials have not been combined because one used UDCA (tablets, 250 mg) at a dose of 13 to 15 mg/Kg/d in four divided doses while the other used a different dosage form (capsules, 200 mg) and dosage schedule (14 mg/Kg/d administered as a single dose). Therefore, safety data gathered from these two trials are presented separately. An additional point of clarification is that serum chemistries and CBCs in the Mayo Clinic trial were obtained every 3 months for possible toxicity. But in the Canadian Multicenter trial AEs were recorded at the 3- and 6-month visits only. The principal investigator judged that AEs beyond 6 months were not related to test medication. Therefore, in the latter trial, there was no systematic evaluation of AEs after the 6-month follow-up visit.

1. Mayo Clinic Trial

a. Extent of exposure

The double-blind portion of this study was initiated in April 1988 and terminated in May 1992 when the 132nd patient randomized into the trial had completed 2 years of double-blind observations. Data were truncated at 2 years for patients maintained on double-blind for more than 2 years (patients randomized early into the trial were maintained on double-blind for 4 years).

- A total of 180 patients had been enrolled into the trial when the study was unblinded in May 1992.
    - 112 of the 180 randomized patients completed at least 24 months of exposure to test medication (UDCA, n=63; PL, n=49).
- As shown in detail in the text of this review, the two treatment groups were reasonably balanced relative to demographic and histologic baseline characteristics and other parameters, including concomitant diseases and concomitant medications.

b. Summary of Safety Findings

- As shown below, at 24 but not at 12 months, the proportion of patients experiencing toxicity was statistically significantly higher in the UDCA than in the PL group:

Visit (months)	UDCA	PL	Treatment Group Comparison (p-value)
12	4 (5%)	8 (9%)	N.S.
24	9 (10%)	0 (0%)	0.002
Overall	13 (15%)	8 (9%)	N.S.

- As shown below, there was no statistically significant difference in the incidence of any of the individual AEs at 12 or 24 months between the two treatment groups.

ADVERSE EVENTS	VISIT AT 12 MONTHS		VISIT AT 24 MONTHS	
	UDCA n (%)	PL n (%)	UDCA n (%)	PL n (%)
Diarrhea	---	---	1 (1.32)	---
Elevated Creatinine	---	---	1 (1.32)	---
Elevated Blood Glucose	1 (1.18)	---	1 (1.32)	---
Leukopenia	---	---	2 (2.63)	---
Peptic Ulcer	---	---	1 (1.32)	---
Skin Rash	---	---	2 (2.63)	---

NOTE: Those AEs occurring at the same or higher incidence in the PL as in the UDCA group have been deleted from this Table [this includes diarrhea and Thrombocytopenia at 12 months, nausea/vomiting fever and other toxicity].

- There were neither deaths nor withdrawals due to drug toxicity during this trial. New or unexpected drug toxicities did not occur.

- As summarized below, a total of 7 patients (UDCA, n=3; PL, n=4) underwent dechallenge/rechallenge. The pruritus cases were probably manifestations of the natural course of this symptom in PBC. Also, the red spots on tongue were related to the underlying condition rather than AEs:

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REASON FOR DECHALLENGE/RECHALLENGE	n	COMMENT
UDCA GROUP (N=3)		
• Pruritus	2	In one case, test med. was gradually re-introduced with no further problems. In the other, the patient discontinued due to persistent pruritus despite reduced dosage and co-administration of cholestyramine.
• Red spots on tongue	1	Symptoms cleared upon reducing the dose. Dosage increased to desired level with no further problems.
PL GROUP (n=4)		
• Diarrhea	1	Patient maintained on reduced dose of 2 tablets/day with no further problems.
• Increased bilirubin	1	Levels returned to normal upon discontinuation. Test med. re-introduced at desired level with no further problems.
• Fever, GI complaints	1	Test med. gradually re-introduced with no further problems.
• Abdominal discomfort	1	Test med. gradually re-introduced with no further problems. Discomfort later attributed to post-liver biopsy pain.

- Significant changes to endpoint from baseline were reported for the below listed non-hepatic laboratory data. But none of these findings were reported as AEs.

	UDCA	PL
Increased	Creatinine TG	Creatinine Calcium
Decreased	Cholesterol Platelets Calcium Total thyroxine WBC Bone Mineral Density[a]	Cholesterol Platelets

a) BMD% did not change.

2. The Canadian Multicenter Trial

a. Extent of exposure

A total of 222 patients were exposed to test medication for a maximum of 733 days at a maximum dose of 14 mg/Kg/d UDCA, administered in a single bedtime dose as 250 mg capsules or matching PL.

- 166 of the 222 patients enrolled (UDCA, n=89; PL, n=77) completed the full 730 days of treatment.

- As shown in detail in the text of this review, the two treatment groups were reasonably balanced relative to demographic and histologic baseline characteristics and other parameters such as concomitant medications for concurrent diseases [except for anxiolytics use, which was significantly higher in the UDCA group, $p<0.005$, an imbalance that is not expected to have an influence on safety results].

b. Summary of Safety Findings

- As shown below, except as noted for increased pruritus, there were no statistically significant differences in the incidence of AEs between the two Tx groups. At 3 but not at 6 months, the proportion of patients experiencing biliary/abd. pain was statistically significantly higher ($p=0.04$) in the PL group than in the UDCA group (data not shown). At 6 but not at 3 months, a higher proportion of UDCA-treated patients experienced increased pruritus than PL-treated patients [$p=0.03$].

APPEARS THIS WAY ON ORIGINAL

Symptoms, Side Effects and Problems	3 MONTHS		6 MONTHS[a]		p-value
	UDCA	PL	UDCA	PL	
	n (%)	n (%)	n (%)	n (%)	
GASTROINTESTINAL					
Nausea/Vomiting	10 (9.0)	5 (4.5)	11 (9.9)	8 (7.2)	
Dyspepsia	5 (4.5)	1 (0.9)	5 (4.5)	3 (2.7)	
Constipation	4 (3.6)	---	4 (3.6)	---	
OTHER					
Increased Pruritus	7 (6.3)	2 (1.8)	9 (8.1)	2 (1.8)	0.03 (6 months)
Headache	3 (2.7)	1 (0.9)	4 (3.6)	3 (2.7)	
Dizziness	2 (1.8)	1 (0.9)	2 (1.8)	1 (0.9)	
Sweating	2 (1.8)	---	2 (1.8)	---	
Anxiety/Depression	4 (3.6)	1 (0.9)	6 (5.4)	3 (2.7)	
Sleep disorder	3 (2.7)	1 (0.9)	4 (3.6)	1 (0.9)	
Joint/Muscle back pain	6 (5.4)	5 (4.5)	---	---	

a) The proportion of patients reporting a specific AE during the 6-month follow-up visit represents cumulative data on these experiences.

<u>NOTE:</u> Those AEs occurring at the same or higher incidence in the PL as in the UDCA group have been deleted from this Table [diarrhea, increased bowel action, biliary/abdominal pain, flatulence and skin rash].

- There were no deaths due to drug toxicity. None of the 14 deaths occurring during the trial (UDCA, n=5; PL, n=9) were attributed to test medication.

- As summarized below, a total of 10 patients (UDCA, n=4; PL, n=6) were withdrawn from the trial due to "suspected" ADRs [the "suspected" term supposedly means that the reported ADR could be related to test medication or could be associated with the progression of the underlying disease].

Age, Sex	Baseline Histologic Stage	Date of Entry/Withdrawal Details of Withdrawal
UDCA GROUP [n=4]		
67 F	N/A	24-Aug-88/16-Sep-88 Nausea, vomiting, abdominal pain that resolved when test medication stopped: recurred on rechallenge.
69 F	II	5-Aug-88/25-Apr-89 Nausea, dizziness, diarrhea.
48 F	III	2-May-90/1-Jun-90 Fatigue, pruritus, change in complexion.
45 F	III	11-Oct-89/27-Jun-90 Intolerable pruritus since entry, resolved when test medication stopped: recurred on rechallenge.
PL GROUP [n=6]		
62 F	IV	27-Jul-88/11-Oct-88 Nausea
37 F	II	14-Mar-89/29-Sept-89 Skin lesions that resolved when test medication was stopped: new lesions on rechallenge.
72 M	IV	17-Mar-89/12-Feb-90 Skin lesions that resolved when test medication was stopped: new lesions on rechallenge.
57 F	I	5-Mar-90/18-Apr-90 Intolerable pruritus, skin rash within one week of starting test medication.
60 F	IV	8-Sep-88/6-Jun-90 Abdominal pain, diarrhea attributed to test medication.
58 F	IV	23-May-90/29-Jan-91 Intolerable pruritus, increase in bilirubin (coincided with start of Voltarin, known for hepatic reactions).

- New or unexpected drug toxicities did not occur.

B. Safety Data from Published Literature on PBC Patients

The reviewer agrees with the sponsor's statement that clinical studies conducted to date in patients with PBC have demonstrated that UDCA is well tolerated and safe. UDCA appears to be almost devoid of side effects and in a fashion similar to that shown in both the critical (Mayo Clinic) and supportive (Canadian Multicenter) trials, the individual literature reports clearly show the absence of drug-related toxicity. A brief summary from individual literature reports, with dose and length of administration of UDCA, is given below.

1. [R. Poupon et al. Lancet 1:834-836 (1987)]

In 1982, these authors initiated an uncontrolled pilot study on the effect of UDCA, administered at a dose of 13 to 15 mg/Kg/d in 15 patients with PBC.

- Transient headache in one patient and transient exacerbation of pruritus (which may have been due to the natural course of the disease) were the only AEs reported.

2. [R. Poupon et al., NEJM 330:1342-1347 (1994)]

These authors reported results of a 2-phase study. Phase 1 was a 2-year, randomized, double-blind, 2-arm, PL-controlled study carried out at several centers throughout France (total n=145). Patients were treated with either UDCA (13 to 15 mg/Kg/d) or matching PL. Phase 2 was an extension of Phase 1: after completion of the double-blind period, all patients were switched to an additional 2-year long-term, open-label follow-up period.

- In this trial, there were no discontinuations due to AEs.
- Transient increase in the severity of pruritus in one UDCA-treated patient occurred upon initiation of the double-blind phase of the trial. There were no other AEs reported in the UDCA-treated group.

3. [U. Leuschner, Scand. J. Gastroenterol. 204(Suppl):40-46 (1994)]

This author was one of the first investigators that showed that UDCA was safe and well-tolerated in hepatitis and PBC patients (see below). In the publication listed above, he reviewed results of 11 controlled clinical trials conducted in a total of 1004 patients treated with doses of UDCA ranging from 8 to 15 mg/Kg/d. All individual authors of these publications reported UDCA to be safe.

C. Safety Data from Published Literature on Other Indications

1. [U. Leuschner and M. Leuschner, Dig. Dis. Sci. 30:642-649 (1985)]

These authors were among the first investigators that reported that UDCA is safe and well-tolerated. They published the results of a two-year study conducted in 6 patients with gallstones suffering from chronic active hepatitis. These patients were treated with UDCA at a dose of 8 to 11 mg/Kg/d for 3 to 20 months. Four patients served as controls. No AEs were reported during the trial or during the follow-up period. There was neither deterioration in general well-being nor abnormalities in laboratory parameters.

2. [R.A. Rubin et al., Ann. Intern. Med., Aug. 1, 121:207-218 (1994)]

These authors reported the results of a metanalysis from published randomized, controlled clinical trials on the use of UDCA in gallstone dissolution or chronic liver diseases, including PBC. They concluded that UDCA had been exceedingly well tolerated with few AEs reported.

3. [C.L. Rosenbaum and R.J. Cluxton, Drug Intelligence and Clin. Pharm. 22:941-945 (1988)]

These authors estimated that diarrhea - the most frequently reported AE in gallstone dissolution trials - occurs in 0 to 4% of the patients treated with UDCA for gallstone dissolution. This is a much lower incidence than the 25 to 50% (often leading to cessation of therapy) reported with CDCA. In this patient population UDCA has been found to be devoid of hepatotoxic potential with no significant effect on liver transaminases. Nonetheless, in some gallstone patients, a transient increase in AST has been reported within the first 3 months of treatment initiation.

4. [A. Ward et al. Drugs 27:95-138 (1984)]

These authors also described the safety profile of UDCA in gallstone patients. It was noted that considering the long-term nature of therapy with UDCA, the drug has been associated with a remarkably low incidence of AEs, especially when compared to CDCA (chenodiol). In several of the trials reviewed by Ward, no AEs were reported even following up to 6 to 12 months treatment with UDCA. In other trials, AEs were infrequently reported. These AEs included: constipation, allergic reaction, itching, headache, dizziness, gastralgia, abdominal pain, pancreatitis and bradycardia. Although LFT abnormalities were occasionally reported, as a rule, serum transaminases, AP and BIL levels were unaltered or even improved.

5. <u>Other Study Populations</u>

UDCA has also been reported to have a good safety profile in patients with varied conditions such as PSC, hepatitis C, nonalcoholic steatohepatitis, autoimmune hepatitis, alcoholic cirrhosis, liver graft rejection, chronic graft-versus-host disease, cystic fibrosis, and hypercholesterolemia.[54]

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[54] [R.E. Poupon and R. Poupon: Ursodeoxycholic Acid for Treatment of Cholestatic Diseases in: J.L. Boyer and R.K. Ockner eds. Progress in liver disease. Eastbome, UK: W.B. Saunders Company, pp 219-238 (1992)]
[G. Paumgartner et al., editors, Bile Acids as Therapeutic Agents; P. Bettner et al., Chapter 42, pp. 345-348 and C. Colombo et al., Chapter 43, Kluwer Academic Publishers, Dordrecht (1991); M.B. Fennerty, Postgrad. Med. 94:81-88 (1993); V. Balan et al. Mayo Clinic Proc. 69:923-929 (1994); R.E. Poupon et al. NEJM, 330:1342-1347 (1994)].

i) Pediatric Patients with Chronic Cholestasis

Initial results reported by W.F. Balistreri et al. have shown that, in 60 children with chronic hepatobiliary disease, UDCA (15 to 30 mg/Kg/d) was well tolerated. There were no significant side effects noted.

NOTE: This information is included here for completeness but it is not applicable to the clinical condition of interest. This is because PBC has never been described in childhood or adolescence. This is a highly unusual feature for which there is no explanation.

ii) Patients With Intrahepatic Cholestasis of Pregnancy

[G. Paumgartner et al., editors, Bile Acids as Therapeutic Agents, J. Palma et al., Chapter 39, Kluwer Academic Publishers, Dordrecht, pp. 319-322 (1991)]

In 6 patients with intrahepatic cholestasis of pregnancy, J. Palma et al. showed that UDCA (mean dose 14 mg/Kg, t.i.d. for ca. 20 days before delivery) was well tolerated in late pregnancy and showed no apparent toxicity in the mothers or in their babies. There is need to expand studies of this type to PBC patients of child-bearing potential. After all ca. 90% of PBC patients are females, some of them, of child-bearing potential.

D. Concerns Based on the Long-Term Administration of Bile Acids (UDCA)

If approved for the treatment of PBC, UDCA would need to be taken long-term - probably for the rest of the patient's life. This subsection briefly considers selected pre-clinical and clinical data related to the subject UDCA and cancer. The implications of the known metabolism of BAs are that, in addition to long-term colonic effects, effects of this drug may be exerted in the liver per se and, owing to possible spillover of the UDCA or its metabolites in the systemic circulation. Long-term effects may be seen in systemic organs, such as the breast and kidney. One source of confusion when interpreting data is that the metabolism of BAs in animals is different from that in man.[55] Consequently, extrapolation of findings in experimental animals must be made with extreme caution and with the realization that, in most (although not in all) instances, the available human data may not confirm the concerns arising from animal experiments.

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[55] No animal species is relevant to man. The rabbit is full of bacteria and therefore produces metabolites different from those produced by humans. The same can be said of rats and mice. A reasonable species to use is the hamster bile because the BA composition of this species is identical to man. The best species is the monkey and the worst the dog. This is because the latter has trouble excreting UDCA. The dog does hydroxylate and, since little is known about BA metabolism in this species, it is the less desirable animal. In addition, CDCA (per se) may be toxic to the dog. In this species, the side effects are seen very soon after the administration of UDCA, before it is converted to LCA.

From the classic experiments of B.S. Reddy et al. [Cancer Res. 37:3238-3242 (1977)], it is known that a number of BAs have co-carcinogenic[56] (promoting) effects in the colon of F344 rats treated topically with MNNG (N-methyl-N^1-nitro-N-nitrosoguanidine). MNNG is a direct acting (an initiator) carcinogen.[57] One important difference between UDCA and the BAs primarily implicated as having colonic cancer promoting effects is that UDCA is not cytotoxic to the colonic epithelial cells [V.S. Chadwick, J. Lab. Clin. Invest. 94:661-674 (1979)]. In fact, as pointed out in the PD Section of the MO review, in erythrocytes and hepatocytes, UDCA **protects against the cytotoxic effects of DCA and CDCA** [Y. Koga et al., Acta Hepato. Japan. 28:1597-1604 (1987); U. Leuschner et al., Gastroenterology 97:1268-1274 (1989)]. Similarly, studies by the group headed by Dr. David Earnest (University of Arizona) have demonstrated that in the azoxymethane model of experimental colonic carcinogenesis, **UDCA was not a tumor promoter**. When added to a promoting dose of CA (0.2% as dietary supplement), UDCA prevented enhancement of tumor promotion and at higher doses (0.4%), UDCA significantly reduced the incidence of colon tumors and cancers. The tumor suppressive effects of 0.4% UDCA exceeded those of dietary piroxicam, a known chemopreventive agent in this model.

From the above, it is clear that the issue of BAs vs colon cancer remains unsettled. In humans, conflicting data have been reported. E. Bayerdorffer [Gastroenterology 104:145-151 (1993)] reported an increase in the serum levels of DCA in patients harboring colonic adenomas. Some studies have shown a positive correlation between increased fecal BA levels and colorectal cancer and/or adenomatous polyps but several others have not [reviewed by Dr. Earnest]. Also, although some epidemiological studies in humans have reported an increase of colon cancer after cholecystectomy - an operation that enhances fecal BA excretion [G.W. Hepner et al., Gastroenterology 66:556-564 (1974)] - other have not. Actually, J. Berkel et al [Amer. J. Gastroenterol. 85:61-64 (1990)] reported a decreasing risk with increasing interval between cholecystectomy and date of diagnosis of colon cancer. These authors have hypothesized that the apparent association between cholecystectomy and colon cancer does not reflect a necessary cause-effect relationship, but is rather an epiphenomenon representing a diminished exposure level to other etiologic factors. It is to be noted that Dr. Earnest and his co-workers are presently carrying out a study in humans, assessing the effects of UDCA on adenomatous polyp recurrence.

There exist reports in the literature suggesting an increased incidence of extrahepatic malignancies among women with PBC. In a retrospective review of 85 PBC patients, P.R. Mills et al. [J. Clin. Pathol. 35:541-543 (1982)]

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[56] A co-carcinogen increases the tumor promotion rate or the tumor formation effect; it does not have carcinogenic properties by itself; it accelerates the neoplastic process only in the presence of carcinogens.

[57] A carcinogen is a compound capable of initiating cancer; it possesses intrinsic carcinogenic properties. Examples include 3-methyl cholanthrene. 1,2-di-Methyl-hydrazine. azoxy methane, N-methyl-N^1-nitro-N-nitroso-guanidine, nitrosamines. nitrosamides, benzopyrines, among others.

reported an observed number of tumors, primarily cancer of the breast, 3.5 times more common than the expected age-adjusted incidence among these patients from Scotland. From an additional retrospective review of 520 patients with cirrhosis of varying causes, these investigators concluded that patients with PBC appeared to be more at risk of developing extrahepatic malignancy than cirrhosis patients in general. Of 208 patients with PBC, followed for one month to 15.9 years by A.M. Wolke and her associates [Amer. J. Med. 76:1075-1078 (1984)], the incidence of breast cancer was 4.4 times ($p<0.01$) the incidence expected from the rate prevailing in the same age range in a comparable normal Connecticut population, thought to be representative of the northeast distribution of the study group. In this study, the incidence of cancer in sites other than the breast and of primary hepatocellular tumor was not significantly increased. These epidemiological findings appear to have been corroborated by additional studies in Scotland by a different group [R.S.C. Rodger et al. BMJ 291:1597-1598 (1985)]. The latter authors studied the occurrence of extrahepatic malignancy in 195 unselected patients who satisfied predetermined biochemical, immunological and histological criteria for the diagnosis of PBC. The incidence of breast cancer in women with PBC was found to be significantly higher than in an age and sex matched control population from the same well defined geographical area ($p<0.0015$).

The above-summarized suspected "positive" association is to be contrasted to the lack of association in a study [A. Floreani et al., Ital. J. Gastroenterol. 25:473-476 (1993)] aimed to analyze the incidence of malignancies in a large series of PBC patients from Italy. The overall sample included 178 patients (10 M, 168 F). The mean age at presentation was 52 y (range 29-74); 17 patients had histological stage I, 52 stage II, 66 stage III, 44 stage IV. The follow-up period ranged from 1 to 16 y (mean 5 y). During the follow-up, extra hepatic malignancies developed in 6 cases (3.3%), and hepatocellular carcinoma (HCC) in a further 4 patients, all associated with cirrhosis (2.2%). Breast cancer developed only in one patient, resulting in a crude incidence rate of 130/100,000 person years among females. The calculated crude incidence of HCC was 492.4/100,000 person years. Three of the four patients with HCC had a superinfection with HCV. These investigators concluded that the incidence of breast cancer **was not significantly increased**. HCC had a relatively high prevalence in PBC and HCV superinfection may play an important role in favoring HCC.

From the above, the reviewer concludes that the issue whether there is an increased incidence of breast cancer in PBC patients is also unsettled. On the meantime, it is worth considering some reports that appear to link bile acids, particularly metabolites, to carcinogenesis. P.R. Baker et al. published a study suggesting that GCDC and unconjugated CDC influence the growth and steroid receptor function of (estrogen-regulated proteins) MCF-7 human breast cancer cells [Br. J. Cancer (UK) 65:566-572 (1992)]. This report is of interest because GCDC is the major human serum BA. In another study, R.W. Owen et al. [J. Steroid Biochem. 24:391-394 (1986)] described the analyses of BAs in colorectal cancer patients, breast cancer patients and healthy control subjects. Fecal excretion of total BAs was similar in the three groups. The major BAs detected were LCA and DCA and the proportions of these (LCA:DCA ratio). were diametrically opposed in the colorectal cancer patients (1.91+ or -0.33) and control subjects (0.9+ or -0.09). Patients with adenocarcinoma of the breast also exhibited a higher LCA:DCA ratio (1.24+ or -0.10) than the control group. These investigators proposed the fecal LCA:DCA ratio as an important marker of cancer risk especially cancer of the large bowel and suggested that it may be a useful adjunct to future screening procedures. Using GL chromatography of the acetoxy methyl esters of the BAs prepared after alkaline hydrolysis of the bile salts, the group of investigators headed by N.B. Javitt identified LCA and other BAs in human breast cyst fluid (BCF) [U. Raju et al. J. Clin. Endocrinol. Metab. 70:1030-1034 (1990)]. **The levels of BAs in serum samples were low.** The levels of BAs in breast cyst fluid were all higher (sometimes 100 times greater) than those in the serum, as follows:

	Micromol/L	Remarks
DCA	17-160	• Detected in 11/12 samples of BCF
CDCA	18-305	"
CA	3-119	"
LCA	9-23	• Detected in 6/12 samples of BCF • Confirmed by MS

The findings by the Javitt's group are of interest because this was the first report of the presence of LCA ("a reported co-carcinogen") in BCF with confirmation by MS. This group of investigators proposed a breast-gut connection since, in their studies, BCF contained BAs that are characteristically found in the intestines. That the BAs originated from the gut was established by giving two patients deuterium-labeled CDCA (three 200 mg doses by mouth), starting 9 days before aspiration of the breast cysts [N.B. Javitt et al., Lancet 343:633-635 (1994)]. For total BAs the cyst/serum concentration ratio ranged from 16 to 38 in cysts from patient 1 and from 48 to 93 in patient 2. For CDCA, the mean concentration rates were 20 and 86, respectively. In both patients, DCA formed a greater proportion of cyst-fluid BAs than of serum BAs.

It is to be noted that in this report by Javitt et al. LCA was found in both patients' serum samples (0.6 and 0.4 μmol/L) but **was not detectable in cystic fluid**. This appears to be a contradiction of previous findings by the same group of investigators. Therefore, the findings by Javitt et al. of higher concentration of LCA in BCF need to be confirmed and expanded. Accurate methods to reliably detect LCA, its amidates (with Gly or Tau) and its conjugates (glucuronate and sulfate) are needed. The implication of the reports by Javitt et al. is that high concentration of BAs in the BCF represents high concentration of the BAs in mammary gland tissue. But in reality, no reports have been published of examination of breast biopsy to determine tissue concentration of LC and the other BAs. The issue at hand is that of **lithocholic acid accumulation** and this is further addressed below.

In one of the publications by N.B. Javitt mentioned above [Hospital Practice (1992)] this investigator proposed that in PBC patients being administered UDCA long-term, there is accumulation of LCA in the patient's liver which will result in **hepatotoxicity**. This would occur either because some of the metabolites that are formed are, in fact, hepatotoxic or because the ability to metabolize LCA is severely limited. Mention was made of heterogeneity in human populations with respect to drug metabolism and the existence of significant individual variation with regard to the disposition of the LCA that is extracted by the liver. Although these appear to be reasonable proposals, they are not supported by the scientific facts briefly considered below.

Recently, the subject of species differences in BA metabolism was comprehensively reviewed by A.F. Hofmann et al. [BAs in liver disease, Ed. by G. Paumgartner and U. Beuers, Kluwer Academic Publishers, Dordrecht, Chapter 1, pp. 3-30 (1996)]. D.M. Neuman demonstrated that the hydrophilic UDCA is hepatoprotective and that hydrophobicity of a BA is positively correlated to its cytotoxicity [Gastroenterology 104:1865-1870 (1993)]. It is true that, in all animal species studied thus far, the inclusion of LCA in the diet causes severe cholestatic liver disease that is not entirely reversible with removal of the BA. As pointed out by A.F. Hofmann in a letter to the editor [Hospital Practice 27:24-26 (1992)] in every case in which LCA toxicity has been observed in animals there has always been a several-fold increase in the proportion of LCA in biliary BAs. But the cholestasis occurs because - unlike humans - **animals do not sulfate LCA**. The sulfation of this metabolite by the liver, renders the compound non-toxic because sulfation promotes excretion (from the body) by various routes, mainly the stools. Sulfated LCA is not absorbed by the ileal transport system for conjugated bile acids. As a consequence, LCA is rapidly eliminated.

In a publication by now classical, R.L. Fisher et al. [Hepatology 14:454-463 (1991)] tested whether hepatotoxicity occurring in NCGSS patients was caused by a toxic effect of chenodiol per se or LCA caused by defective sulfation.[58] Samples were obtained from NCGSS patients (n=17) with abnormal light microscopic liver Bx results or major aminotransferase elevations and from a matched control group of patients (n=14) who received similar chenodiol doses but had no evidence of liver injury. Bile samples from 45 healthy subjects were also analyzed. No significant differences were seen between gallstone patients with and without evidence of liver injury for % total lithocholate amidates, percent sulfated or nonsulfated lithocholate amidates or % chenodiol

[58] Bile samples were analyzed using a [redacted] method that measures the proportions of the four individual lithocholate amidates (sulfated and unsulfated lithocholylglycine and lithocholyltaurine) and all common BA amidates.

amidates. Lithocholate was partially sulfated in all bile samples [52% ± 17% (mean ± S.D., n=50)] but the extent of sulfation varied widely between and within patients during the course of therapy. Mean values of healthy subjects were similar and also showed a wide range in the extent of lithocholate sulfation. Fisher et al. concluded that liver injury caused by chenodiol was due directly or indirectly to the chenodiol but could not be attributed to the accumulation of unsulfated lithocholate per se in circulating BAs.

The above-summarized data originated from gallstone patients and one could argue with good reason that this is not the target population subset of the present NDA. But this information is presented to demonstrate that, LCA accumulation (in whatever form) is not resulting in toxic effects to the liver. Unfortunately, neither in the pivotal nor in the supportive PBC clinical trials in NDA 20-675 were levels of LCA or LCA metabolites measured in liver tissue. But whatever this amount and whatever high binding affinity this BA may have for liver parenchyma (proposed but not proven by Javitt), it can be argued with reasonable certainty that LCA is not accumulating in toxic amounts. This is because, in a significant number of UDCA-treated patients, **all signs of cholestasis went down** and at 4 years, there was a significant effect on clinically important parameters. Another indirect demonstration of the lack of toxicity of LCA arising from UDCA administration is in the use of the latter BA in the treatment of Intrahepatic cholestasis of pregnancy (ICP). As reported by J. Palma et al., UDCA therapy appears to be effective in most cases with ICP. Pruritus and serum levels of BAs and transaminase improved significantly during this treatment [Hepatology 15:1043-1047 (1992)].

It follows that, for any clinical condition where UDCA may be administered, the most important determinant to prevent LCA-related toxicity seems to be the **ability to sulfate lithocholic acid.** In considering the target population being treated with UDCA, toxicity due to LCA may not occur in certain groups of patients. The first group consists of those that lack bacterial flora. Lack of bacterial flora would likely occur in patients that have had a resection of the ascending colon as well as in those receiving agents such as antibiotics or lactulose that alter the colonic flora. This subset of patients will not form LCA. Two additional groups, proposed by Javitt, consist of those who produce considerable amounts of LCA but absorb little from the intestine and those who absorb considerable amounts of LCA, which is then extracted from the portal circulation by the liver but is subsequently metabolized to less toxic derivatives. Javitt proposes that it is in this last group that LCA hepatotoxicity can occur, either because some of the metabolites that are formed are, in fact, hepatotoxic or because the ability to metabolize LCA is severely limited. But there are neither studies evaluating the absorption of LCA in liver disease patients receiving UDCA nor documented cases of inability to sulfate LCA in PBC patients.[59]

Some information on serum LCA derived from the Mayo Clinic trial.[60] The following is summarized from the publication of results of a study by M.A. Lacerda et al. [Liver Meeting, Chicago (1993)]. This study was set to define the relationship between fasting-state serum BAs (SBAs) and biliary BAs (BBAs) in PBC patients ingesting UDCA (n=22) or PL (n=14) for 2 years. Serum was obtained after an overnight fast, with the last dose of UDCA taken the preceding evening. Bile was obtained at endoscopy later that morning.[61] As reported within the text of this review, there was no correlation between biliary and serum BA composition. This lack of agreement resulted from discrepancies in two BAs.

- In half of the samples, SBAs had high LC (5 to 35%).
- Whereas in BBAs LC was <2% in all but one sample.
- In one-third of the samples, SBAs UDCA was 30 to 70% when UDCA in BBAs was <10% (ratio serum to bile = 3 to 7).

These interesting data suggest that, in some PBC patients, there is incomplete extraction of UDCA by the liver. Whether the retention of UDCA (et al., namely LCA) in the liver of PBC patients is the same or higher than in those without cholestatic liver disease is not known. But a higher concentration of BA in serum than in bile[62] has also been reported after administration of UDCA in pediatric children with chronic cholestasis:

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[59] As pointed out by A.F. Hofmann, the inability to sulfate LCA has been identified in only two gallstone patients ingesting UDCA; and most cases of CDCA hepatotoxicity do not result from LCA accumulation or its impaired sulfation. Impaired sulfation of lithocholic acid causing its accumulation with resultant hepatotoxicity has not been reported in any gallstone patient ingesting UDCA: there are probably at least 300,000 patient-years of experience. Were gallstone patients to have defective sulfation of UDCA, they would be likely to show laboratory evidence of cholestasis and inflammation and an increased proportion of LCA in their biliary BAs. based on the animal studies cited. As noted, there is no evidence on the basis of the limited number of analyses of biliary bile acids reported to date for impaired sulfation of LCA in patients with chronic cholestatic liver disease. This is in keeping with the premise that LCA does not accumulate in biliary BAs when UDCA is administered.

[60] Apparently, there was no assessment of serum LCA and its metabolites, amidates and conjugates in the Canadian Multicenter trial.

[61] SBAs were determined

[62] During treatment for gallstone dissolution, Whiting and Watts observed the mole percentage of UDCA in serum to be 2 to 4 times higher than in bile. In contrast, the relative concentrations of CDCA were observed to be very similar in bile and serum [Gastroenterology 75:220-225 (1980)].

UDCA enrichment. The average percentage and [range] UDCA in serum and bile before and after >4 weeks of UDCA therapy (15 mg/Kg per day) in patients with extrahepatic biliary atresia (n=13)

	Serum UDCA	Biliary UDCA	Serum/Bile Ratio
	percentage of total bile acids [ ] = range		
Baseline	0.6 [<0.1 to 2.0]	2.1 [<0.1 to 6.8]	0.29
UDCA therapy	37.0 [33 to 43]	14.0 [2.5 to 30]	2.64

Modified from: W.F. Balistreri et al. Biochemical and clinical response to ursodeoxycholic acid administration in pediatric patients with chronic cholestasis. in Bile Acids as Therapeutic Agents; G. Paumgartner, A. Stiehl, W. Gerok, eds.; Kluwer Academic Publishers, London, pp. 323-333 (1991).

As repeatedly pointed out in the present review, SBAs are the result of a spillover of BAs from the EH into the systemic circulation. Since the individual BAs differ in their intestinal absorption and hepatic uptake [B. Angelin & I. Björkhem, Gut 18:606-609 (1977); B. Angelin et al., J. Clin. Invest. 70:724-731 (1982)], it is really not surprising that their proportions in bile and serum are not identical [M.J. Whiting and J.M. Watts, Gastroenterology 78:220-225 (1980)]. As previously mentioned, current available data are consistent with the view that, in PBC patients, first-pass hepatic extraction for UDCA is ca. 50%, according to the Paumgartner group [G. Miescher et al., Eur. J. Clin. Invest. 13:439-445 (1983)].

In conclusion, an appreciable concentration of LCA, sometimes higher than in the bile, is to be expected after administration of UDCA to some PBC patients. The Mayo Clinic evaluations involved solvolysis-deconjugation followed by GLC. It is important to know to what extent LCA in the serum remains deamidated and/or non-sulfated and/or non-glucuronided. But this information can be obtained. Although some uncertainty remains due to incomplete information, there is no experimental evidence in support of Javitt's speculation that LCA binds to tissues. On the contrary, **there is strong indirect evidence that LCA does not accumulate in liver parenchymal**. Whether LCA binds to mammary gland tissue is not known. Although the Javitt's group has published preliminary data suggesting that LCA can be identified in human breast cyst fluid, some of their interesting findings appear to contradict their own reports. Thus, the Javitt's data are yet to be confirmed. Once confirmed, these data should be expanded. In this section of the MO review, the role of sulfation of LCA in humans, as opposed to animals in which LCA is hepatotoxic, was emphasized.

XII. RECOMMENDATIONS FOR REGULATORY ACTION

1. On the basis of the evidence presented by the sponsor of NDA 20-675, the reviewer recommends approval of UDCA for the treatment of patients with all stages of primary biliary cirrhosis.

   - This recommendation is based, primarily, on the results of the well-designed and well-executed Mayo Clinic trial. The Mayo Clinic trial results (Lindor et al.) are supported by those from the Canadian Multicenter trial (Heathcote et al.).

   - The recommended dose for UDCA in the treatment of PBC is 13 to 15 mg/Kg/day administered in four divided doses with the three main meals and at bedtime.

2. Thus far, all trials in PBC and many other liver-related indications strongly suggest that long-term administration of UDCA to the target population(s) is well tolerated and safe.

   Nonetheless, there are some lingering concerns (mostly hypothetical) about high levels of LCA in the serum of PBC patients administered UDCA and speculations that this BA metabolite may bind to tissues and exert co-carcinogenic effects. In addition, possibly as a result of the UDCA formulation used, pre-malignant/cancerous lesions were shown in the urinary tract of rats treated lifelong with this bile acid, in a study conducted by Dr. U. Leuschner. The reviewer recommends to address both of these issues in the labeling.

September 19, 1996

/S/ [redacted]

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-675
HFD-180
HFD-180/SFredd
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
r/d 8/9/96 jgw
f/t 9/16/96 jgw
MED\N\20675609.0HG

9/19/9 [redacted] APPEARS THIS WAY ON ORIGINAL

/S/ [redacted]

TABLE 52
The Canadian Multicenter Trial

Patients Withdrawn at the Request of the Investigator

ID# Age, Sex	Baseline Histologic Stage	Date of Entry	Date of Withdrawal	Details of Withdrawal
A. UDCA-treated Patients [n=2][a]				
04-1036 67 F	IV	17-May-89	9-May-90	Complications due to PBC; recurrent GI bleeding, anemia, repeated hospitalization.
07-1003 65 F	II	18-Apr-89	10-Dec-90	Complications due to PBC; hepatic coma
B. PL-treated Patients [n=2]				
04-1007 52 M	II	15-Jun-88	6-Dec-89	Esophagectomy for esophageal carcinoma; could not swallow capsules.
01-1026 44 F	I	14-Mar-90	26-Sep-90	Primary lymphoma of the bowel with involvement of the spinal column and central nervous system, undergoing radiotherapy, unable to absorb medication.

a) These two patients who were experiencing severe PBC symptomatology, were not eligible for transplantation at the time of their withdrawal.

13. Sponsor's Conclusions

"The study included 222 patients with primary biliary cirrhosis, 166 of whom completed the two-year treatment period (89 in the UDCA group and 77 in the placebo group). The results of this trial indicated the following:

- "UDCA at a dosage of 14 mg/kg per day for two years was significantly more effective than placebo in slowing the progression of primary biliary cirrhosis as judged by laboratory markers of cholestasis. UDCA delayed treatment failure in this population without regard to histologic stage or symptomatology, and in patients with baseline bilirubin less than or equal to 1.8 mg/dl (31 μmol/L).

- "UDCA at the above dosage appeared to be generally safe and well-tolerated in this patient population."

E. Reviewer's Comments on the Canadian Multicenter Trial

The Canadian Multicenter trial was submitted by the sponsor of NDA 20-675 as providing **supportive** (not pivotal) data for the approval of UDCA tablets for the treatment of patients with all stages of PBC. This non-US trial was well designed. The study included two parallel arms. One arm was a dose of UDCA, 13 to 15 mg/Kg, taken in capsule form to the nearest 250 mg swallowed whole with the evening meal. The other arm consisted of PL, an adequate negative control. From the in-depth review of the evidence, consisting of very detailed information submitted by the sponsor, the MO concludes that the study was well-executed. The trial was conducted under double-blind conditions. In addition to double blinding, other measures were taken to minimize bias on part of the investigator and other individuals involved with observations and analysis of data from this trial. Also, the experimental subject did not know the identity of the medication she/he was taking. The primary objective of the trial, prospectively stipulated in the protocol, was to compare the effects of UDCA and those of PL on the percentage rise in serum bilirubin level at 24 months. The primary hypothesis was that UDCA exerts a beneficial effect in the steady rising of bilirubin, **a very reliable laboratory marker of cholestasis**. Significant decrease in other markers of cholestasis such as bile acids, γ-glutamyl transpeptidase, AP and serum transaminases were also expected after 2 years of treatment.

Because of the 2-year cutoff this trial did not have sufficient follow-up to assess the effects of UDCA therapy on clinically meaningful endpoints such as survival and/or the need for liver transplantation. But a number of secondary objectives were listed in the protocol (see comments below). Also carried out was an *ad-hoc* evaluation of the effect of UDCA on treatment failure and a comparison of these effects to those seen in the patients treated with PL.

The 222 patients selected in a 1:1 ratio for this trial (UDCA=111; PL=111) had a primary diagnosis of PBC. This condition was defined as confirmed cholestatic liver disease, elevated serum AP levels (for the local laboratory), positive AMA_8 test (AMA_8 titer ≥1:20) and liver biopsy in the previous 12 months diagnostic of or compatible with the diagnosis of PBC. Patients were initially stratified according to whether they were symptomatic or asymptomatic. Immediately following this stratification, the patients were randomized to one or the other arm of the trial. Symptom criteria for stratification included pruritus, variceal bleeding or jaundice. In this trial, adherence to the protocol-stipulated inclusion-exclusion criteria precluded randomization of patients with diseases, conditions or concomitant treatments that may confound the results.

In the Canadian Multicenter trial, the randomization process accomplished two well-balanced groups with respect to a number of important variables. Data showing comparability of groups at baseline included the stipulated number of patients (111 per group), primarily (>91%) female patients, similar mean age and weight, ratio of symptomatic (ca. 87% of the patients) to asymptomatic patients, individual symptoms (jaundice, fatigue, pruritus, xanthelasma, variceal bleeding, ascites), hepatic biochemical markers (total serum bilirubin, AP, transaminases, PT, albumin), immunoglobulins (IgM, IgA, IgG), AMA_8 titer and serum cholesterol. The two experimental groups were also similar to each other in the distribution of hepatic histological stage. It is important to note that, in the Canadian Multicenter trial, liver biopsies were staged I through IV on the basis of the degree of **fibrosis**: stage I=no fibrosis; stage II=periportal fibrosis; stage III=fibrosis with septa and stage IV=cirrhosis. So, the emphasis with this scale was on fibrosis. This is to be contrasted to the Ludwig's scale used in the Mayo Clinic trial. As discussed above, the latter combined fibrosis with necroinflammatory activity. In the Canadian Multicenter trial, five further histological parameters were graded on a scale of 0 (none), 1 (mild), 2 (moderate) or 3 (severe). These histological parameters included lobular lymphoid inflammation, portal lymphoid inflammation, duct paucity, ductular proliferation and periportal (or paraseptal) hepatocellular ballooning (feathery degeneration). Duct paucity was graded as 0, all ducts present; 1, occasional ducts present; 2, up to half of ducts absent; and 3, more than half of ducts absent. Pretreatment and posttreatment liver biopsies were paired at the end of the trial and a comparison analysis was performed. For each parameter, the difference in pretrial and posttrial score was tabulated as improvement (down 1 or more grades), no change, or progression (up 1 or more grades). Except as noted, the two treatment groups were also balanced in regards to concomitant medications. At baseline, a higher proportion of patients in the UDCA group were taking anxiolytics. Although mentioned here for the sake of completeness, this statistically significant imbalance ($p<0.005$) is not expected to have a significant impact on the efficacy results.

As in the Mayo Clinic trial, for most biochemical parameters of evaluation UDCA produced divergent trends from those induced by PL. At the end of the 2-year trial, the mean (or median) values for serum bilirubin changed in opposite directions: worsening of the PL group while the UDCA group was improving. In comparison to PL, UDCA treatment reduced a) the proportion of patients experiencing an increase in serum bilirubin of >50% (therapeutic gain=19%; $p<0.001$), and b) the percent change in bilirubin (median therapeutic gain=37%, mean therapeutic gain=60%; $p=0.0001$). This superiority of UDCA over PL was demonstrated in patients with early (I & II) or late (III & IV) histologic stage as well as in those who were symptomatic at baseline. For the parameters AP (therapeutic gain=45%), AST (therapeutic gain=45%), ALT (therapeutic gain=53%), IgM (therapeutic gain=19%) and CHOL (therapeutic gain=16%), the percent changes to endpoint from baseline among the UDCA-treated patients were all statistically different from those seen in the PL-treated group.

Using an *ad hoc* definition of treatment failure (see text of review), UDCA was shown to significantly decrease the proportion of patients failing (therapeutic gain=25%; $p<0.001$). UDCA also significantly prolonged (therapeutic gain=3.6 months, $p\leq0.007$) the mean time to treatment failure. When examining effects on strata, this superiority of UDCA over PL was shown in the stratum of patients with baseline bilirubin of ≤1.8 mg/dl and the stratum with late histologic stage (III& IV). But neither the stratum with bilirubin >1.8 mg/dl at baseline nor that stratum of patients with early (histologic stage I & II) disease showed these changes.

Not unexpectedly, mainly because demonstration of an effect would require extended periods of treatment (i.e. 4 or more years), the results from the Canadian Multicenter trial did not show differences between UDCA and PL in the