NDA

019368

AP

LTR

cc: Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-100/Dr. Temple HFN-232 (with labeling)
HFN-110/CHeald/9/13/85;9/18/85;10/25/85
cb/9/13/85;sb/10/28/85/0534v
R/D Init: PDeslauriers/9/[illegible]/85
CResnick/9/20/85 submitted
NRosenthol/9/20/85
AThompson/9/25/85
HMorgenstern/9/25/85
CHeald/9/18/85, 9/25/85
RLipicky/9/26/85
WBachRach/9/26/85

APPROVAL

NDA 19-368

OCT 29 [illegible]

Ascot Pharmaceuticals, Inc.
Attention: Mr. Arnold M. Schacter
7701 N. Austin Ave.
Skokie, IL 60077

Dear Mr. Schacter:

Please refer to your new drug application dated September 1, 1984 submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Moctain (monooctanoin).

We also acknowledge receipt of your amendments dated August 9, September 6, 12, 26 and 27, 1985.

We have completed the review of this application including the submitted draft labeling, and the application is approved. Prior to marketing, however, please add the statement "Not for Intravenous Administration" to the immediate container and carton labels and revise the package insert exactly as indicated in the enclosed draft. Please submit twelve copies of the final printed labels and other labeling seven of which are individually mounted on heavy weight paper or similar materal.

While all other aspects of this application have been found to be approvable, the required validation of the analytical methods has not been completed but is ongoing in our laboratories. In such a case the policy of the Center for Drugs and Biologics is to proceed with approval.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved application set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Cathy Heald
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

RT 10/28/85
10/28/85
WH 10/28/85

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure

CHeald 10-25-85

10/28/85

10/28/85 RT

OCT 28 1985

AE

LTR

NDA 19-368

Ascot Pharmaceuticals, Inc.
Attention: Mr. Arnold M. Schacter
7701 N. Austin Ave.
Skokie, IL 60077

Dear Mr. Schacter:

Please refer to your September 21, 1984 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Moctanin (monooctanoin).

We also acknowledge receipt of your amendments dated February 11, May 7, June 24, and July 1, 1985.

We have completed the review of this application and it is approvable pending satisfactory inspection of your manufacturing facilities and submission of revised labeling for the drug. The labeling should be revised as shown in the attached draft and in addition, as follows:

The draft labeling does not convey an adequate sense of the risks of therapy with monooctanoin and is defective in several sections: Clinical Pharmacology, Warning, Precautions, and Adverse Reactions. First, there is good evidence from animal and human studies that monooctanoin is very irritating to the gastrointestinal and biliary tracts. The animal and human (e.g., Geenan, Venu, et al and others) data should be included in labeling, preferably under clinical pharmacology. The Adverse Reactions section should then discuss the consequences of this irritability (see below).

Second, the major risk of the drug appears to relate to ascending cholangitis, presumably related to obstruction of the common bile duct, and perhaps because of insufficient attention to the infusion pressure of monooctanoin. The phenomenon should be fully discussed in labeling. It may be suitable to consider it briefly under Clinical Pharmacology as a theoretical matter, but it should then be discussed as a Warning describing briefly the range of side effects seen and providing advice on what to do if evidence of cholangitis is seen. The Warning section should mention the absolute need for controlling infusion pressure with an overflow manometer and refer to the Dosage and Administration section for instructions on how to do this.

The Adverse Reactions section should provide greater detail and an indication of the seriousness of adverse effects seen. One way to do this would be as follows

1. List of adverse drug reactions and frequency:

Adverse Reaction	N = (number exposed) No. of Reactions (frequency)
(List in order of frequency under reasonable headings such as GI, systemic effect, etc.)	(Give the absolute number and the frequency where frequency = $\frac{\text{number}}{\text{n exposed}}$)

The list should include all adverse drug reactions reasonably likely to be drug related. It may be helpful to have a brief paragraph preceeding the list describing the most frequent and most serious reactions.

2. Discussion of specific adverse drug reactions or groups of adverse drug reactions, such as a) the GI irritability, duodenal ulcer group, b) symptoms representing ascending cholangitis. (Alternatively, instead of describing these groups of reactions under this section, they could be described in full under the Warnings section and the Adverse Reactions section can simply refer to the discussion under Warnings).

3. The adverse drug reactions that were severe enough to lead to discontinuation of therapy should be identified, either as part of the overall list or in a separate section.

4. Adverse drug reactions not seen in the multicenter trial but reported in the literature should be cited.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and a second copy, with a copy of the package insert, directly to the Director, Division of Drug Advertising and Labeling (HFN-240). Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit twelve copies of the printed labels and other labeling seven of which are individually mounted on heavy weight paper or similar material.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Cathy Heald
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

R Temple 7/31/85

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-240 (with draft labeling)
HFN-83
HFN-100/Dr. Temple
HFN-110/CHeald/5/9/85;6/27/85;7/26/85
cb/5/9/85;sb/7/26/85;7/26/85/0311v
R/D: init: RLipicky/5/10/85
WBachrach/6/12/85
NRosenthan/6/14/85
RWolter/6/14/85
CResnick/6/27/85
DPresley/6/27/85
NMorgenstern/7/26/85 pam 7/26/85
RTemple/7/26/85

APPROVABLE

R T 7/28/85

Wolter 7/30/85

WA 7/30/85

SBA

Summary Basis of Approval

NDA 19-368

Drug Generic Name:
Monooctanoin

Applicant:
Ascot Pharmaceuticals, Inc.
7701 N. Austin Avenue
Skokie, IL 60077

Drug Trade Name:
Moctanin

I. Indications for Use:

Moctanin (monooctanoin) is indicated as a solubilizing agent for cholesterol (radiolucent) gallstones retained in the biliary tract following cholecystectomy, when other means of removing cholesterol stones retained in the common bile duct have failed or cannot be undertaken.

Treatment results in complete stone dissolution about one-third of the time and in reduction in stone size in approximately another one-third of patients. When reduced in size, these stones may pass spontaneously or may be more susceptible to physical extraction. Complete dissolution is much more likely when there is a single stone (almost 50%) than when there are multiple stones (about 20%). For unclear reasons, complete dissolution is uncommon in diabetic patients (about 10%).

II. Dosage form, route of administration and recommended dosage:

Moctanin is a clear, viscous, sterile liquid administered as a continuous perfusion through a catheter inserted directly into the common bile duct generally via a T-tube or through a nasobiliary tube placed endoscopically.

Perfusion should be at a rate of 3.0 to 5.0 ml/hour at a pressure of 10 cm H_2O. Duration of perfusion of monooctanoin is from 7 to 21 days. If, after 10 days, endoscopy or X-ray shows neither elimination or reduction in size of stones, therapy should be discontinued.

III. Manufacturing and Control:

A. Manufacturing and Controls

The active drug substance is purchased as a mixed mono-di-glyceride from another firm. The preparation of the drug substance is described in sufficient detail

with supporting data. Adequate specifications and tests are provided for the release and acceptance by the manufacturer of the drug product to assure the identity, strength, quality and purity of the drug substance.

The controls over the manufacturing procedures and the drug product give adequate assurance of the identity, strength, quality and purity of the drug product.

B. Stability

The applicant has submitted satisfactory stability data in support of the drug substance and the drug product in their respective containers. The stability data support a 24 month expiration dating period for the drug product packaged in a borosilicate glass bottle with a particular closure. A two year storage period at room temperature is established. Appropriate provisions are made to continue stability studies and to withdraw from the market any lots of the drug product that may become outside the standards for acceptance.

C. Methods Validation

While all other aspects of this application have been found to be approvable, the required validation of the analytical methods has not been completed - but is ongoing in our laboratories. In such a case the policy of the Center for Drugs and Biologics is to proceed with approval.

D. Labeling

The proposed labels and other labeling are in accord with the technical requirements pertaining to the proprietary name, the established name, ingredient statements, expiration dating period, prescription caution statement, applicant's name and address, and conditions for drug product storage.

The "Description" and the "How Supplied" sections of the package insert are satisfactory. The proprietary name is not in conflict with the name of any other drug product.

E. Establishment Inspection

Verification of the operations of the facilities involved in the preparation of the drug substance and manufacture of the drug product, and conformance with Current Good Manufacturing Practice Regulations and

procedures described in the New Drug Application have been requested.

F. Environmental Impact Analysis Report

The applicant provides an environmental impact statement that there will be no significant impact on the environment due to the manufacture and use of the drug product.

IV. Pharmacology:

Monooctanoin is a semi-synthetic mixture of medium chain glycerides formed from the reaction of glycerol with medium chain fatty acids derived from coconut oil. The medium chain fatty acids are predominantly caprylic acid and capric acid. The mixture is similar to an approved GRAS OTC nutritional supplement (MCT) manufactured by Mead Johnson.

When monooctanoin enters the intestine from the perfused biliary tract, it is hydrolized by pancreatic and intestinal lipases mainly to glycerol, caprylic acid, and capric acid. The glycerol and medium chain fatty acids released in the digestion of monooctanoin are absorbed, metabolized and excreted just as are the digestion products of ordinary coconut or the marketed OTC nutritional supplement.

Numerous in vitro tests showed that monooctanoin completely dissolves or significantly reduces the size of cholesterol stones in just a few days and is significantly more effective than sodium cholate or heparin, two other cholesterol solubilizing agents. Monooctanoin is much less effective against bilirubin stones.

In a Federal Register Notice dated December 10, 1982, the FDA Orphan Products Development Office invited the submission of a new drug application for use of monooctanoin in dissolving residual cholesterol gallstones after a cholecystectomy. That Notice acknowledged the existence of four published animal studies relevant to the proposed use of the drug (each of these studies described in the Ascot application) and spelled out a requirement of only one more animal test:

> "a 4-week common bile duct perfusion study in dogs, including gross and histopathologic examination of the duodenum and stomach. The reversibility of the expected irritation should also be defined."

The Gadacz dog study, reported in the Ascot application, appears to be an attempt to satisfy the above request. The

rate of infusion was, however, only 1/5 of the proposed maximum human rate of 5 ml/hr and the duration of infusion only about 1/4 the proposed maximum human duration of 21 days. Deficits in magnitude and duration of exposure are also identifiable in the four other nonclinical safety studies described in the application. Each of the five studies alluded to above are briefly summarized as follows:

A. Common Bile Duct Infusion in Dogs (T.R. Gadacz, M.D.):

Two cholecystectomized mongrel dogs were infused continuously into the common bile duct for five days with 1 ml monooctanoin per hr. (1/5 the maximal clinical rate); another two were similarly infused but sacrificed 14 days after cessation of the infusion. Four cholecystectomized controls were given saline and one was simply sham operated. Tissues examined histologically at term included the distal part of the common bile duct, the antral area of the stomach immediately proximal to the pylorus, the duodenum distal to the entrance of the common bile duct at the Ampulla of Vater, a random section of the liver, and a proximal or mid-portion of the pancreas. Hepatic and pancreatic enzymes were analyzed at time of operation, beginning of infusion, and at end of infusion.

The sham operated dog and four saline treated dogs showed no clinical chemistry disturbances related to the infusion. None of the four monooctanoin treated dogs showed serum amylase changes, but two of the dogs showed liver enzyme elevations that may have been related to the infusion; one of these dogs (#5) showed slight elevation of SGOT and alkaline phosphatase at the end of infusion that was not apparent before the infusion, and the other dog (#4) showed marked elevations of SGPT and alkaline phosphatase and moderate elevations of SGOT and serum bilirubin during infusion that had essentially disappeared 14 days after infusion (pre-infusion values were not recorded; this dog showed foci of hepatic necrosis histologically).

Grossly, there were no significant changes in the common bile duct, stomach, duodenum, liver, or pancreas. No ulceration, erosion, erythema, friability, or stricture was visibly evident in any of the bile ducts.

Histologic examination did not reveal pathological changes in the pancreas, duodenum or stomach of monooctanoin treated dogs. The dog that showed mild liver enzyme changes exhibited mild hepatic congestion and the dog which showed marked enzyme changes exhibited

focal areas of hepatic necrosis. Whereas the common bile duct of saline treated dogs showed only mononuclear cell infiltration, of the monooctanoin treated dogs also showed proliferation of the mucosa (3/4) and inflammation (some fibrosis) of at least a mild sort (2/4). The diameter of the common bile duct was comparable (average 6 mm) in all animals except for one monooctanoin treated dog (12 mm).

B. Common Bile Duct Infusion in Monkeys (Mack et al, ACS Surgical Forum, 1978, 29: 439):

Five monkeys were infused with monooctanoin through a T-Tube into the common bile duct (CBD) for up to a month and a half at 2.6 ml/hr (half the maximum clinical rate).

Monooctanoin was said to have caused mild to moderate inflammation of the CBD in 4/5 monkeys, but no pancreatitis, diarrhea, or deaths.

C. Gallbladder Infusion in Cats (Schenk et al, Gastroenterology 1979, 76:1237):

Seventeen adult cats weighing 1.7 - 2.8 kg were anesthetized with pentobarbital sodium (30 mg/kg i.p.). After median laparotomy, a Teflon tube was inserted in the gallbladder. Monooctanoin was infused via catheter either continuously at a rate of 3 ml/hr for 4, 6, 8 hours once (group A, n=10), or intermittently for 4 hours daily over a period of 4 days at a rate of 0.6 ml/hr (group B, n=5). In each group one animal was perfused with 0.9% NaCl for control. The animals were killed immediately after treatment and the liver, pancreas, gallbladder, common bile duct, and Vater's papilla were examined histopathologically in serial sections.

Depending on the contact time, inflammatory epithelial damage, like acute oedematous destruction of the biliary and papillary mucosa (group A) or cellular infiltration of the submucous layer as well as acute pancreatitis in two cases (group B), as found in the animals treated with monooctanoin while no pathological findings were noted in the controls. The authors concluded that "cholangitis, papillitis, and possibly acute pancreatitis due to repeated contact with monooctanoin as seen in our animal model has to be taken into account when choosing this mode of treatment in patients with common bile duct stones."

D. Liver (Left Heptic Lobe) Injection in Rats (Sharp et al, ACS Surgical Forum, 1981, 32:176-177):

In this experiment, designed to study the intrinsic hepatotoxicity of the drug, 0.1 ml of monooctanoin, sodium cholate, or saline induced the appearance of necrotic, hyalinized centers surrounded by fibrosis in the livers of 6/10, 17/17 and 0/8 (adult) animals, respectively. "Nine of the 10 monooctanoin treated rats died from hemorrhagic pneumonitis within 30 minutes of injection." None of the sodium cholate or saline treated rats died.

E. Heindenhain Gastric Pouch Infusion in Dogs (Lillimoe et al, Surg. Gyn. Obstet., 1982, 155:13-16):

In this experiment, performed to evaluate potential for gastric toxicity in patients who may experience reflux of drug into the stomach, infusion of monooctanoin into the Heidenhain pouches of 6 Mongrel dogs caused disruption of the gastric mucosal barrier. This was evidenced by dose related increased net hydrogen ion flux and dose related loss of electronegativity of transmucosal electrical potential difference. No evidence of gross hemorrhage was observed.

Injury to the gastric mucosa has been observed with bile acids (after hepatitis, the most common lesion in animals treated orally with chenodeoxycholic acid is gastrointestinal irritation and ulceration).

V. Medical:

A. Introduction:

As discussed in the Federal Register (Volume 47, pages 55520-55522, 1982), the Orphan Products Development Office invited submission of a new drug application for monooctanoin to be used in the in situ dissolution of residual cholesterol gallstones subsequent to cholecystectomy. Monooctanoin is a mono-di-glyceride that is formed from the esterification of glycerol with caprylic and capric acid. A substantial number of published in vitro studies provide a rationale for the use of this agent for dissolving residual gallstones.

Thistle et al (1,2) was the first to demonstrate that the calculus dissolving capacity of monooctanoin was approximately 3 times greater than sodium cholate after 72 hours incubation in vitro (Figure 1).

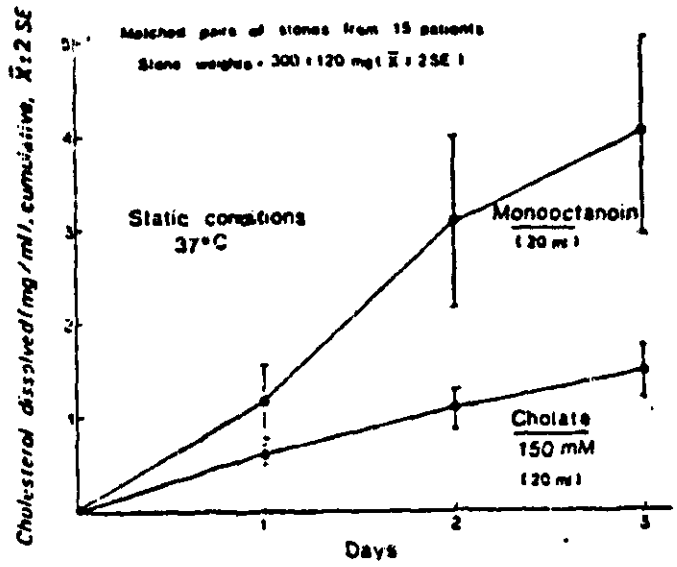


Figure 1. Dissolution rate of cholesterol from matched gallstones (average precalculation wt. 300 mg) in monooctanoin or 150 mM cholate.

This observation was partially confirmed by Gadacz (3) who showed that gallstones placed in 100 ml of monooctanoin lost 87% of their weight by day 4. On the other hand, 300 mM sodium cholate and heparin at 100 units/ml produced a 33% or negligible reduction in stone weight, respectively, after 10 days of incubation (Figure 2).

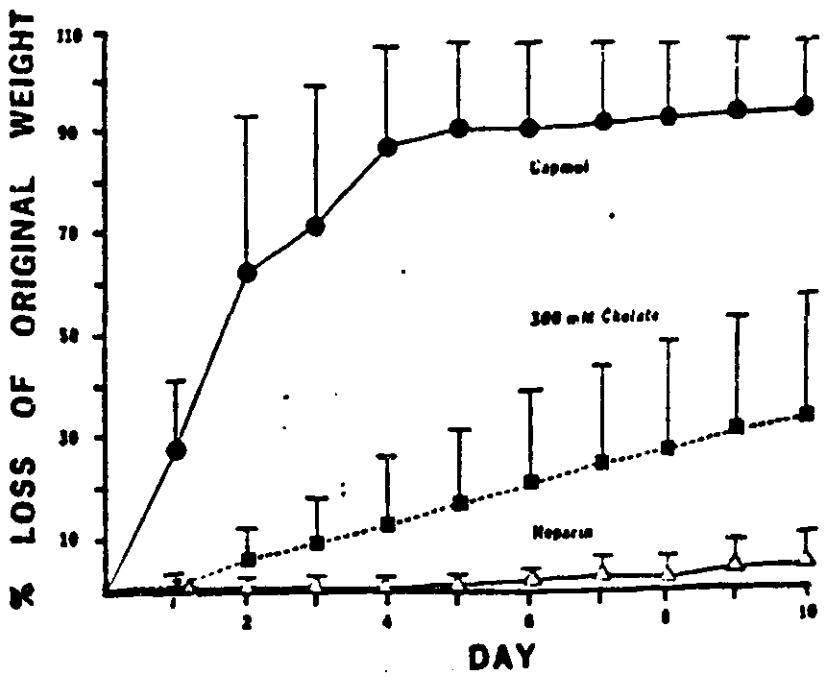


Fig. 2. Each point represents the mean and standard deviation of six gallstones from six different patients. The percentage reduction of the stones in the monoctanoin solution is statistically different from the cholate or heparin solution (P<0.0005) for all values.

Similarly, Antenzana et al (4) observed a 60% weight reduction in bile duct stones after 3 days in monooctanoin and 100% by day 14. This is in contrast to 6 and 12% decrease in stone weight after 14 days in 100 units/ml heparin or 200 mM sodium cholate, respectively. In this latter study (4), the cholesterol concentration of each test solution was determined at 3,6, and 14 days and found to be inversely proportional to stone weight, suggesting large stones tend to dissolve more slowly, irrespective of the dissolving medium. By day 14, 100% of total cholesterol in each stone was solubilized by monooctanoin, while 22% of the total bilirubin present in stones of mixed composition was also solubilized.

A number of workers have confirmed that the disintegration of bile duct calculi in monooctanoin is dependent on both stone composition and size. Sharp and his colleagues (5) found that only 1 of 14 stones low in cholesterol (0-10%) could be dissolved in monooctanoin, and the time required in the one instance of dissolution was 8 days (Figure 3).

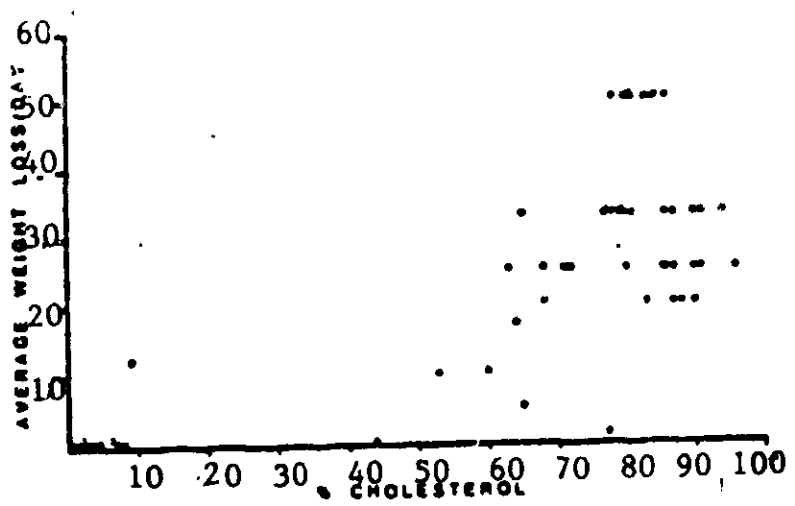


FIG. 3. The rate of dissolution is compared with the cholesterol content of each stone. The rate of dissolution was greater in the group of stones high in cholesterol compared with those stones low in cholesterol ($p < .001$).

Conversely, stones having in excess of 40% cholesterol dissolved at the rate of 30% per day, with 91% of these stones ultimately dissolving completely. In a study by Teplick et al (6) of biliary calculus dissolution in monooctanoin, heparin (1000 units/ml), sodium dehydrocholate, or saline, monooctanoin was the only agent in which calculi dissolved completely (Table.1).

TABLE 1: Percentage Responses to Gallstone Dissolving Agents

Agent	Partial or Complete Dissolution	Complete Dissolution	Loss of 50% Weight in 2 Weeks or Less
Monoctanoin	98	71	83
Cholic acid	27	0	18
Heparin	6	0	0
Saline	17	0	0

Of the stones that did dissolve, 49% did so within the first 2 weeks and 50% dissolved within 3 weeks. In addition, most of the stones exposed to monooctanoin became soft and could easily be crushed. Black (bilirubinate) stones were not affected by monooctanoin, while the presence of calcium in stones was associated with longer dissolution times and a reduction in the number of stones actually dissolving in this agent. Larger stones (greater than 1 cm) also tended to dissolve more slowly, with only 45% dissolving completely, in contrast to 83% of the small (less than .5 cm) stones.

The relationship between stone size and extent of dissolution in monooctanoin was also explored by Venu et al (7). They observed that after 14 days of incubation in monooctanoin, 4 stones initially weighing 60, 88, 190, and 242 mg, respectively, were reduced to 0, 8, 24, and 41% of their initial weight (Table 2).

Table 2

In Vitro Dissolution of Gallstones by monoctanoin.

Initial Stone Wt (mg)	Stone Wt in mg and (% of Initial Wt) on Day:			
	4	7	11	14
242	168 (69)	131 (54)	107 (44)	100 (41)
190	112 (59)	57 (30)	46 (24)	45 (24)
88	42 (48)	38 (43)	9 (10)	7 (8)
60	30 (50)	20 (33)	2 (3)	0 (0)
$\bar{x} \pm SE$ of 1%	57 ± 5*	40 ± 5*	20 ± 9*	18 ± 9*

* $p < 0.05$ compared to initial stone weight of 100%.

Finally, Tritapepe and his associates (8) collected gallstones from 9 subjects and incubated them for 4 days with 20 ml of monooctanoin at 37°C under static conditions. Two of these stones fragmented by 4 days while the remainder were reduced in weight from 4 to 54%(Table 3).

Table 3
In Vitro Dissolution of Retrieved Gallstones by Monooctanoin

Patient No.	Initial Stone Wt	Stone Wt after 4 Days of Incubation	
	mg	*mg*	*% of initial wt*
2	180	108	60
7	205	151	74
8	107	103	96
9	125	67	54
10	93	Fragmented	
12	174	147	84
13	148	101	68
14	131	89	68
15	150	Fragmented	

The two stones composed of 12 and 32% bilirubin, respectively, exhibited only a 16 and 4% reduction in weight, which is consistent with the results of several studies discussed above (4,6). Parenthetically, Uribe et al (9) has shown that in vitro gallstone dissolution in monooctanoin is not appreciably accelerated by incubating under dynamic, as opposed to static, conditions (Figure 4).

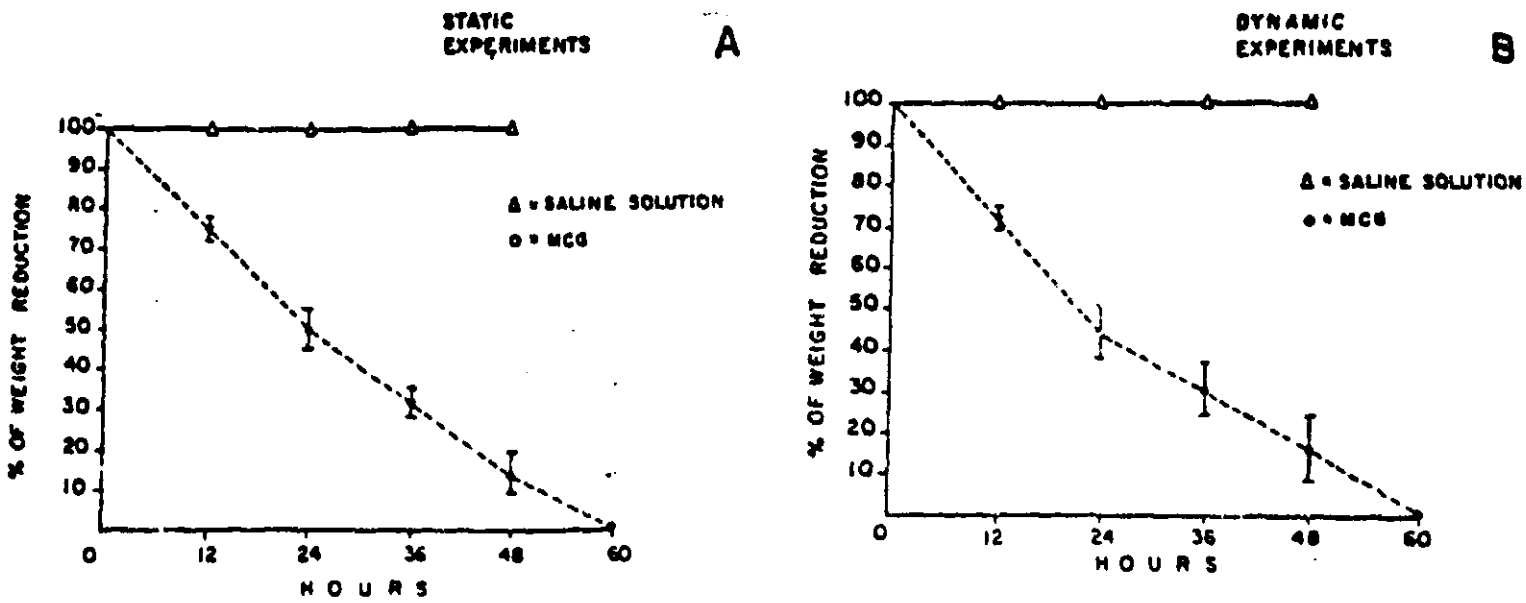


Fig 4 Static (A) and dynamic (B) *in vitro* incubation of cholesterol gallstones showing rapid dissolution with MCG while stones remained unchanged with saline solution. In both cases differences between MCG and saline incubation were significant ($P < 0.05$ at 12 hr and $P < 0.01$ at 24, 36, and 48 hr).

In conclusion, a multitude of studies have demonstrated that monooctanoin is capable of dissolving bile calculi in vitro at a rate that is dependent on both calculus size and composition. Smaller stones and those predominantly composed of cholesterol (and not bilirubinate) tend to dissolve more rapidly and completely. Monooctanoin has also been shown to be a more effective medium for dissolution of bile calculi than sodium cholate, heparin, or saline. The ability of monooctanoin to dissolve cholesterol stones in vitro has served as the basis for in vivo testing of the agent by numerous clinical investigators in patients with residual common bile duct stones. The results of these efforts will be described in the succeeding sections.

B. Multicenter Study of Monooctanoin

1. Design and Conduct of Study

Monooctanoin has been available for study since 1975, but in 1982 Dr. Alan Hofmann undertook to monitor use of the product by a wide range of physicians under his "master" IND, and data accumulated rapidly. As part of his monitoring, Dr. Hofmann spoke to each prospective physician user assuring appropriateness of patients, understanding of administration technique (particularly use of the overflow manometer), likely side effects, and willingness of the physician to administer the drug according to protocol and complete the case report form.

Patients were eligible for treatment if they had retained radiolucent duct stones, direct access to the bile duct by T-Tube, percutaneous transhepatic catheter, nasobiliary tube, or cholecystotomy catheter. Patients with a grossly infected biliary tree or evidence of parenchymal liver disease were excluded. During cholangiography, dye was to flow freely into the duodenum; if this was not so, monooctanoin was used only when no other approach was possible.

Monooctanoin was used with or without sterile filtration and undiluted or diluted 10% with water to decrease viscosity. It was infused with a constant infusion pump or gravity into the T-Tube, nasobiliary tube, etc, and particular care was

taken to avoid elevated biliary tree pressure, a result of obstructed outflow as might occur in patients with an intact sphincter of Oddi or large common duct stones. This was done by keeping an overflow manometer (CVP Manometer) between the pump and patient, adjusted so that if pressure exceeded 12 cm of monooctanoin, the monooctanoin would overflow from the tube. The recommended infusion rate was 1-2 ml/hr to go to 5 ml/hr, but infusion rates twice that were sometimes used. In some patients with an obstructed common duct, a concentric catheter was used (but ordinarily such patients were not to be treated with monooctanoin).

Cholangiograms were obtained prior to treatment and then at least weekly, and liver chemistries were monitored.

Because the study was carried out by individual investigators in the course of patient care, reporting is not as complete as it is in the usual drug company sponsored studies. Thus denominators for various demographic features may differ because of incomplete reporting. The full analysis of effectiveness data has been performed on the subset (the large majority) of patients with complete data.

2. Results of the Multicenter Study

Patients. A total of 403 patients were treated with monooctanoin between May 17, 1975 and October 5, 1983 by the investigators listed in the Appendix. These patients were divided into two groups depending on whether they were treated in the United States or Canada, or some other country. Most of the patients were from the U.S. (308) with Canada contributing 10 and the remainder (85) being scattered among 13 other countries including West Germany, England, Italy, Sweden, Denmark, Holland, Netherlands, Ireland, Japan, Korea, Argentina, Chile, and Panama.

Outcome information was available for 377 patients, but sufficient information, useful in the evaluation of the relationship between pretreatment or treatment variables and clinical outcome (Table 4), was available on 274 United States and 52 foreign subjects (326).

Table 4. Clinical Outcome for Patients Receiving Monooctanoin for the Dissolution of Biliary Calculi.

	United States			Foreign			Total			Statistic***
Outcome*	1†	2ß	Total	1†	2ß	Total	1†	2ß	Total	Total
Complete Success	89	8	97	12	11	23	101	19	120	USvF= NSD
Partial Success	84	2	86	5	1	6	89	3	92	USvF=.000(US)
Failure	70	8	78	21	14	35	91	22	113	USvF=.001(F)
Discontinued	31	7	38	14	0	14	45	7	52	USvF= NSD
Grand Total	274	25	299	52	26	78	326	51	377	

* Complete Success: stone(s) disappeared; Partial Success: stone(s) reduced in size, stones disappeared and reduced or no change in size, stones reduced and no change in size: Failure: stones did not change in size; Discontinued: patient discontinued for some reason.

† Patients for whom adequate data were available for inclusion in analyses of relationship between pretreatment or treatment variables, and outcome.

ß No data available except for final outcome.

*** Chi-square analysis was used to compare the proportion of U.S. and foreign patients in each outcome group. Letters (US, F) next to p value denote group with the highest proportion. NSD - no significant difference.

A total of 26 patients (of the 403 treated) were not included in any of the analyses for the reasons given in Table 5.

Table 5. Patients Not Included In Any Statistical Analysis.

Category	Reason	Number of US Patients	Number of Foreign Patients	Total
Technical Failure	Capmul leaked.	3	-	3
	Unstated.	2	-	2
	Removed T-tube.	1	-	1
	Cholecystojejunostomy prevented Capmul infusion.	1	-	1
Misdiagnosis	Patient did not have calculi.	6	-	6
Capmul not administered.	Patient reported side effects before perfusion initiated.	1	-	1
Other	No outcome reported	5	7	12
	Total	19	7	26

Methods. Pretreatment variables (Tables 6, 7, and 8) included sex, age, presence or absence of icterus, location of stone(s), length of time in months (duration), whether the patient had biliary calculi prior to treatment, number and size of calculi, and any accompanying medical condition. Stone location was denoted as proximal (hepatic bile duct, common hepatic bile duct, cystic duct), distal (common bile duct, ampulla of Vater), or in multiple sites within the biliary tree. Duration was surmised from information present in the case records of individual patients. Calculus number was treated as attribute (single or multiple) or continuous (actual number of multiple stones) data. Calculus size (in mm) was provided in the data collection sheets or case records, and was obtained from a cholangiogram taken immediately prior to the initiation of monooctanoin infusion. Concomitant medical conditions were noted and grouped together according to system involvement.

Table 6. Pretreatment Variables For US Patients Who Received Monooctanoin Infusion For Dissolution Of Biliary Calculi

	Sex			Age (yr)	Icteric	Location*			Duration (mo)β	Number of Calculi		Size of Calculi (mm)
Group	M	F	Total			Proximal	Distal	Multiple		Single	Multiple-Actual†	
1. Complete Success	47	35	89	63.8 ± 2.0	13	14	71	4	1.9 ± .4	56	29 - 3.9 ± .9	11.1 ± 1.1
2. Partial Success	31	48	84	61.9 ± 2.3	17	24	66	13	3.1 ± .8	25	59 - 5.1 ± 1.0	17.0 ± 1.6
3. Failure	26	39	70	67.3 ± 2.4	7	16	59	8	3.8 ± 1.7	28	38 - 6.8 ± 3.7	13.1 ± 1.2
4. Discontinued	11	14	31	69.4 ± 3.4	2	7	22	1	3.7 ± 1.5	10	16 - 2.6 ± .3	8.8 ± 1.2
Grand Total (mean ± SE)	115	136	274	64.6 ± 1.2	39	61	218	26	3.0 ± .6	119	142 - 5.1 ± 1.1	13.5 ± .7
Statistics‡	NSD			NSD	NSD	NSD	NSD	NSD	NSD	P 1v2,3,4 = .000 - NSD 2,3,4 = NSD		P 1v2 = .002 1v3 = NSD 1v4 = NSD 2v3 = .029 2v4 = .002 3v4 = NSD

* Calculi were located in either the proximal (hepatic bile duct, common hepatic bile duct, cystic duct), distal (common bile duct, ampulla of Vater) or multiple sites within the biliary tree.

β Length of time in months a patient had biliary calculi prior to treatment.

† Mean (±SE) number of stones in patients with multiple calculi. NSD = no significant difference.

Table 7
Concomitant Conditions Present in US Patients Who Received Monooctanoin Infusion For Biliary Calculi

	Cardiovascular					Respiratory		Endocrine					Musculoskeletal			Digestive			Nervous		Urino-genital	Infection	Other[9]	Total Pts with Condit
Group	CHF	ASHD	Hyper-tension	Arrhy-thmia	Other[1]	COPD	Other[2]	Thyroid Disease	Other[3]	Pancrea-titis	Dia-betes	Other[4]	Rheum-atoid Ar.	Osteo-Arth.	Other[5]	Diver-ticulosis	Hernia	Other[6]	Senile Dementia	Other[7]	Other[8]			
Complete Success	4	8	8	4	4	4	7	2	-	1	2	2	3	2	1	2	2	3	2	2	4	2	2	31
Partial Success	9	6	6	3	2	1	1	1	1	2	5	1	3	-	-	2	4	10	3	3	1	4	5	43
Failure	3	4	7	2	5	-	-	3	-	1	10	-	-	2	1	1	1	5	1	2	-	2	6	27
Discontinued	1	2	1	-	2	1	1	-	-	1	1	-	-	1	1	-	-	1	-	1	2	3	-	12
Grand Total	17	19	22	9	13	6	9	6	1	5	18	3	6	5	3	5	7	19	6	8	7	11	13	113
Statistics†	NSD	NSD	NSD					P 3vs1,2,4 = <.03 1,2,4 = NSD										NSD						NSD

Only conditions with a total frequency ≥5 are listed as discrete subcategories.

1. Angina (3), abdominal aortic aneurism (3), post-myocardial infarct (3), cerebrovascular accident (3), esophageal varices, cardiac arrest.
2. Pleuritis (2), pneumonia (2), emphysema (2), asthma, atelectasis, cystic fibrosis.
3. Thyroid nodule.
4. Pheochromocytoma, pancreatic cutaneous fistula, pancreatic mass.
5. Spinal degenerative disease, polymyopathy, ankylosing spondylitis.
6. Stenotic OBD (3), cholecystocolonial fistula (2), peptic ulcer, T-tube fistula, hepatic abscess, gallbladder hydrops, bile peritonitis, gastric carcinoma, dumping syndrome, subdiaphragmatic abscess, blood clots in biliary tree, cirrhosis, periportal fibrosis, sclerosing cholangitis, melena, malnutrition.
7. Chronic brain syndrome (2), Parkinson's disease (2), paraplegic, schizophrenia, polyneuritis, depression.
8. Acute renal failure (2), renal cyst, renal insufficiency, cervical carcinoma, epididymitis, prostatic hypertrophy.
9. Pruritis (2), retinal detachment,, anemia, deaf, edema, cataract, sickle cell trait, anorexia, hyponatremia, glaucoma, allergies, gross obesity.

† Compares discrete subcategories, having a grand total ≥ 15 patients, by chi-square analysis. NSD = no significant difference.

Table 8. Comparison Of Pretreatment And Treatment Variables In US And Foreign Patients Receiving Monooctanoin For Dissolution Of Biliary Calculi

Variable*		United States	Foreign	Statistics†
Pretreatment				
Sex	Male	115	13	
	Female	136	24	NSD
Age (yr)		64.6 ± 1.2	63.2 ± 2.7	NSD
Location	Proximal	61/254	5/30	NSD
	Distal	218/254	24/30	NSD
	Multiple	26/254	2/30	NSD
Duration (mo)		7.0 ± .6	1.4 ± .3	NSD
Number	Single	119	25	p=.007 (F)
	Multiple	142	11	p=.007 (US)
	Actual	5.1 ± 1.1	5.4 ± 2.3	NSD
Size (mm)		13.5 ± .7	14.8 ± 4.4	NSD
Treatment				
Date		2460. ± 40	1914 ± 72	p=.000
Method	T-tube	170	19	p=.016 (US)
	NBT	54	16	p=.008(F)
	Other	20	3	NSD
Rate (ml/hr)		4.8 ± .1	4.8 ± .5	NSD
Duration (d)		9.4 ± .6	8.3 ± 1.1	NSD

* Pretreatment: Proximal (hepatic bile duct, common hepatic bile duct, cystic duct); distal (common bile duct, ampulla of Vater).

Duration (length of time in months a patient had biliary calculi prior to treatment).

Number (number of patients with single or multiple calculi; actual is mean number of stones ± SE in patients with multiple stones.

Treatment: Date (number of days ± SE from Jan 1, 1975 to the initiation of perfusion). Duration (length of perfusion in days ± SE).

† Data were analysed by chi-square analysis, or analysis of variance (ANOV) and the least significant difference (LSD) test. Letters (US, F) denote the group with the highest proportion.

The date, method, rate, and duration of infusion, along with therapy-induced side effects were the treatment variables included in the statistical analysis (Table 9). The date of perfusion was denoted in days from January 1, 1975. T-tube, nasobiliary tube (NBT), percutaneous transhepatic tube (PTHT), and other were the methods used to infuse monooctanoin. The rate of infusion was given in ml/hr, and length of infusion in days. Side effects were listed under the following subcategories: pain, nausea, emesis, diarrhea, fever, and other (Table 10).

Table 9
Treatment Variables for US Patients Who Received Monooctanoin Infusion For Biliary Calculi

Group	Date*	Method*					Rate* (ml/hr)	Duration (d)*
		T-tube	NBT	PTHT	Other	Total		
1. Complete Success	2952.7 ± 78.7	60	17	-	2	79	4.6 ± .2	7.6 ± .6
2. Partial Success	2457.5 ± 68.5	49	18	4	5	76	4.7 ± .2	14.6 ± 1.7
3. Failure	2583.2 ± 68.3	42	15	3	5	65	4.9 ± .3	8.3 ± .6
4. Discontinued	2499.4 ± 120.6	19	4	-	1	24	4.2 ± .4	2.1 ± .3
Grand Total (mean ± SE)	2460.2 ± 40.8	170	54	7	13	244	4.8 ± .1	9.4 ± .6
Statistics†	NSD	NSD	NSD	NSD	NSD		NSD	P 1v2 = .000 1v3 = NSD 1v4 = .007 2v3 = .000 2v4 = .000 3v4 = .004

* Date (from Jan 1, 1975 in days), method, rate and duration of perfusion.

† Attribute data were analyzed by chi-square, and measurement data by analysis of variance (ANOV) followed by a least significant difference (LSD) test. NSD = no significant difference.

Table 10. Side effects appearing in US patients who received monoctanoin for dissolution of biliary calculi

Group	Pain	Nausea	Emesis	Diarrhea	Fever	Other*	Total pt with side effects	Pt with multiple side effects	Pt without side effects	Total Pt	Symptom Score Severe	Symptom Score Persistent
1. Complete Success	34	36	21	19	6	21	69	43	20	89	3	11
2. Partial Success	40	21	12	13	4	11	62	29	22	84	0	4
3. Failure	29	17	11	17	5	9	50	29	20	70	1	4
4. Discontinued	14	13	7	1	3	6	27	12	4	31	8	2
Total U.S. Only	117	87	51	50	18	47	208	113	66	274	12	21
U.S. & Foreign	139	104	65	63	18	57	251	134	75	326		
Statistics†	NSD	P 1,4v2,3 =.04	NSD	NSD	NSD	NSD	NSD	NSD	NSD		4v1, 2, 3=.000 1, 2, 3= NSD	NSD

* Other includes: Discomfort (20), anorexia (9), loose stool (5), indigestion (2), lethargy (2), increased serum amylase (2), pruritis (2), allergic reaction, headache, depression, chills, burning epigastrum, fatigue, hypokalemia, persistent leukopenia, bile shock, diaphoresis, increased drainage from choledochoduodenal fistula.

† Chi-square analysis was used to compare the incidence, severity and persistence of side effects in the various outcome groups.

It can be seen from Table 8 that there were relatively few differences between the U.S. and foreign cohorts with regard to various pretreatment and treatment variables. The foreign cohort did, however, have a significantly higher proportion of patients with a single calculus (69 vs 46%), was treated earlier than the U.S. subgroup (February 26, 1979 vs August 27, 1980), and had a higher proportion of patients administered monooctanoin with a nasobiliary tube (42 vs 22%). Conversely, the U.S. cohort was treated later, and had a higher proportion of patients with multiple stones and monooctanoin administration via a T-tube (70-50%).

Patients were assigned to one of four clinical outcome cohorts depending on whether the stone(s) (1) completely disappeared during the course of monooctanoin infusion (complete success); (2) were retained, but some either disappeared or were reduced in size (partial success); (3) neither disappeared nor were reduced in size (failure); or (4) neither disappeared nor were reduced in size and the patient and/or physician elected to discontinue treatment (discontinued). The latter two groups (3,4) were considered treatment failures but were kept separate for each of the statistical analyses.

The relative frequency or absolute value of any particular variable in each of the clinical outcome cohorts was contrasted using chi-square analysis or analysis of variance (ANOV), respectively. When more than two proportions were being compared, which was generally the case, the chi-square was partitioned using the method suggested by Fleiss (12) with df=m - 1, where m is the total number of proportions in the original comparison. Statistically significant differences in continuous data between individual groups was assessed by the least significant difference (LSD) test.

Dissolution Rates and Side Effects:

The clinical response in the total patient population was considered complete for 32% of the subjects, partial for 24%, and a failure for 30%, with 14% being discontinued (Table 4). The U.S., in contrast to the foreign study group, had a higher proportion of partially successful patients (29% vs 8%, p less than .000), and a lower proportion of subjects in the failure cohort (26% vs 45%, p less than .001).

Tables 6 and 7 demonstrate that, with the exception of number and size of calculi and the incidence of diabetes, there were no significant differences between the various U.S. clinical outcome cohorts vis-a-vis pretreatment variables. It should be noted, however, that 57% of the complete success subgroup were male in comparison to 39 - 44% of the three other cohorts which was nearly statistically significant (p less than .09). The complete success subgroup had a significantly higher proportion of patients with a single calculus (66% vs 30-42%, p less than .000), while subjects in the

partial success cohort had significantly larger calculi (17 mm vs 9-13 mm, p less than or equal to .03). The incidence of diabetes was greatest in the failure subgroup (Table 4, p less than .03); put another way, only 2/18 diabetics (11%) responded, compared to 32% overall.

Duration of infusion and the incidence of nausea and severe symptoms accompanying monooctanoin infusion were the only treatment variables significantly different among the four clinical outcome cohorts (Tables 9, 10). The duration of infusion was significantly greater for patients in the partial success subgroup (14.6 vs 2-8 days, p less than .000), and significantly shorter for discontinued subjects (2 vs 8 - 15 days, p less than or equal to .007). Patients in the complete success and discontinued cohorts had a higher incidence of nausea (40-42% vs 24-25%, p less than .04), while discontinued subjects reported more severe side effects (26% vs 0-3%).

Medications being taken concomitantly by U.S. patients on monooctanoin therapy are tabulated in Table 11. There was no significant difference among the various subgroups in the proportion of subjects receiving these drugs (range 19-32%). It would seem unlikely, therefore, that monooctanoin-drug interaction is a factor in the determination of clinical outcome for patients receiving this therapeutic procedure.

Table 11. Drugs Given Concomitantly To US Patients On Monooctanoin Infusion For Dissolution Of Biliary Calculi

Congestive Heart Failure	Hypertension - Diuretic - Vasodilator *			Angina
Lanoxin	Regroton	Spironolactone	Vasodilan	Nitrobid
	Ser-Ap-Es	Lasix		Persantine
	Enduronyl	Hydro-Diuril		Isordil
	Dyazide			
	Inderal			
	Catapres			
	Apresoline			
	Rauwolfia			

Arrhythmia	Cardiac Depressant	Analgesic - Inflammation		Ulcer	Thyroidism
Procan	Quinidine	Talwin	Reclomen	Carafate	Thyroid
Pronestyl		Aspirin	Ascriptin	Tagamet	Synthroid
Norpace		Darvon	Trilisate		
Quinidex		Zorex	Prednisone		
		Motrin	Aristocort		
			Naposyn		

Asthma	Diabetes	Cholinergic	Anticholinergic	Mucogel	Gallstone Dissolution
Theo-Dur	Lente	Urecholine	Pro-Banthine	Premarin	Chenodeoxycholic Acid
Aminophyllin	Insulin	Pilocarpine	Correctal	Provera	
Ventolin	Diabinese				

Antibacterial	Nutritional	Mineral	Hypercholesterolemic	Uricosuric
Cephalosporin	Liposyn	Klotrix	Questran	Anturane
Cefonic	Ensure	Iron Sulfate		
Cefadyl		Calcium Gluconate		
Keflex				
Ancef				

Aminoglycosides	Laxative	Diarrhea	Emesis	Antacid
Tobramycin	Peri-Colace	Lomotil	Reglan	Maalox
Gentamycin	Evac-U-Gen		Tigan	
Other	Doxidan			
Flagyl	Sihlin			
Cefoxitin	Metamucil			
Ampicillin				
Clindamycin	Tranquilizer-Antidepressant			Insomnia
Vibramycin	Triavil			Dalmane
Erythromycin	Mellaril			Restoril
	Amitriptyline			
	Meprobamate			
	Librax			
	Valium			

Anticonvulsant
Dilantin

* Drugs listed under clinical indication or product category.

Table 12 delineates the changes observed in serum alkaline phosphatase (SAP) and serum glutamic oxaloacetic transaminase (SGOT) from the beginning to the termination of monooctanoin infusion. Both the SAP and SGOT mean scores were significantly greater in the discontinued cohort subgroup with the SAP mean score being significantly lower in the partially successful subgroup in comparison to the three other cohorts. The discontinued patients' serum enzyme mean scores were substantially greater than 2 (2.63 and 2.7) and the partial success patients' SAP mean score was less than 2 (1.61). Thus there is a tendency for the discontinued subject to have elevated SAP and SGOT, but the partial success subject to have reduced SAP over the course of monooctanoin infusion.

Table 12. Changes in serum alkaline phosphatase (SAP) and glutamic-oxaloacetic transaminase (SGOT) levels in US patients during monoctanoin infusion ofr biliary calculi

Group	Unchanged		Reduced		Elevated		Total		Mean Score[†]		Statistics[β]	
	SAP	SGOT	SAP	SGOT	SAP	SGOT	SAP	SGOT	SAP	SGOT	SAP p	SGOT p
1. Complete Success	30	21	18	26	12	9	60	56	1.90 ± .09	1.70 ± .10	1v2= .023 1v3= NSD	NSD NSD
2. Partial Success	17	24	34	26	10	11	61	61	1.61 ± .09	1.75 ± .10	1v4= .007 2v3= .002	.001 NSD
3. Failure	26	19	8	19	10	8	44	46	2.05 ± .10	1.76 ± .11	2v4= .000 3v4= .034	.001 .002
4. Discontinued	3	2	0	0	5	5	8	7	2.63 ± .18	2.70 ± .19		
Grand Total	76	66	60	71	37	33	173	170				

* Relative difference in serum enzyme levels from the beginning to the discontinuation of Capmul infusion.

† The mean score is derived by multiplying the number of patients in each category by 3 (elevated), 2 (unchanged), or 1 (reduced), summing the 3 values, and dividing by n.

β Data were analyzed by analysis of variance (ANOV), and the least significant difference (LSD) test.

Table 13 lists the reasons for patient discontinuation in both the U.S. and foreign cohort with the most common being severe and/or immediate side effects (47% of the total subjects who discontinued treatment). Among the more serious but infrequent reasons for discontinuation were cerebrovascular accident, renal failure, bile shock, and impacted calculus resulting in obstructive jaundice. Only the latter two conditions could, however, be imputed to monooctanoin infusion.

Table 13. Reasons For Patient Discontinuation

Reason	Number of Patients (US)	Number of Patients (Foreign)	Total
Severe and/or immediate side effects.	12	9	21
Pt refused further Rx.	3	1	4
Side effects of unstated severity.	-	3	3
Not due to Capmul.	3	-	3
No reason given.	2	-	2
Stone impacted, obstructive jaundice.	1	1	2
Pt had cerebrovascular accident.	1	-	1
Pt with sepsis, CHF, and renal failure died after 24hr perfusion.	1	-	1
Bile shock, diaphoresis.	1	-	1
Allergic reaction.	1	-	1
Pressure >15cm.	1	-	1
Liver function enzymes elevated.	1	-	1
Increased perfusion rate, pain.	1	-	1
Pt couldn't tolerate NBT.	1	-	1
T-tube removed.	1	-	1
Stone removed mechanically.	1	-	1
	31	14	45

Discussion

Based on the preceding data, it is possible to construct a descriptive profile of patients receiving monooctanoin infusion for the treatment of biliary calculi. The average age of the subjects in the U.S. cohort was 64.6 years, with more females being treated than males (54 vs 46%) (Table 8). A preponderance of the patients in this cohort had calculi present in a distal as opposed to a proximal position in the biliary tree (86% vs 24%). Three months was the average time that elapsed between the symptomatic occurrence or diagnosis of ductal stones and treatment with monooctanoin. Most of the patients had more than one stone (54%). Those with multiple stones had an average of 5.1. The mean size for the largest stone appearing in individual patients was 13.5 mm. The average treatment date for subjects in the U.S. cohort was August 27, 1980 (Table 9). Most of the patients were given monooctanoin via a T-Tube (70%). Infusion was at an average rate of 4.8 ml/hr for 9.4 days. Forty-one percent of the U.S. cohort had concomitant conditions at the time of monooctanoin infusion (Table 7). Cardiovascular disease was by far the most prevalent concomitant condition with 17 subjects having congestive heart failure, 19 atherosclerotic heart disease, 22 hypertension, 9 arrhythmia, and 13 some other type of cardiovascular involvement. Eighteen patients had diabetes. Monooctanoin-induced side effects were observed in 76% of the U.S. patients (Table 10). The most common was pain (43%) followed by nausea (32%), emesis (19%), diarrhea (18%), discomfort (7%), fever (7%), and numerous other side effects of lesser frequency. The most serious adverse reaction in the other category is probably bile shock which occurred in one patient.

Clinical outcome was judged to be completely successful for 32% of the U.S. patients, while 29% experienced some reduction in size or number of calculi as a consequence of monooctanoin therapy. Twenty-six percent of the subjects were considered failures (no change in stone size), and 13% were discontinued after a mean infusion period of 2.1 days. Data in Tables 8 and 9 provide a basis for speculation on the determinants of outcome in patients receiving monooctanoin for the treatment of ductal calculi. The complete success cohort had

a significantly higher frequency of subjects with a single calculus indicating that complete dissolution-disappearance is more likely when multiple stones (less than or equal to 2) are not present in the biliary tree. Further, the partial success cohort had a significantly longer duration of perfusion than the failure group. This suggests that patients with multiple calculi might derive some clinical benefit if the infusion time is extended from 8.3 (for failures) to 14.6 days. It should also be noted that partial success was attained for patients with multiple stones even though they had significantly larger calculi.

The descriptive profile presented above for the U.S. cohort can be compared to that seen for the foreign patients on monooctanoin therapy (Table 8), but there are actually few substantive differences between these two groups that could explain the better outcome for the US subjects, (Table 4), 32% vs 29% complete success, and 29% vs 8% of partial success. Since the U.S. patients were treated significantly later than their foreign counterparts (Table 8), it is possible that certain refinements in the method of monooctanoin infusion during the intervening 546 days is responsible for the higher proportion of partial success patients in the U.S. cohort. Similarly, a nasobiliary tube may not be as effective as a T-Tube for administering monooctanoin, although this suggestion is probably belied by the rather constant proportion (17-24%) of subjects in the various U.S. clinical outcome subgroups who received this agent via a NBT (Table 9). A more plausible explanation for this difference in clinical outcome is that failure subjects in the foreign cohort may not have been treated for a sufficiently long period of time to attain the dissolution of at least some of the biliary stones. This notion is supported by the fact that failure patients in the foreign cohort were treated for only 7 days (mean), while the partial success patients in U.S. cohort were treated for 14.6 days. Finally, it is conceivable that U.S. physicians are more able or willing to discern the nuances between a partial success and failure.

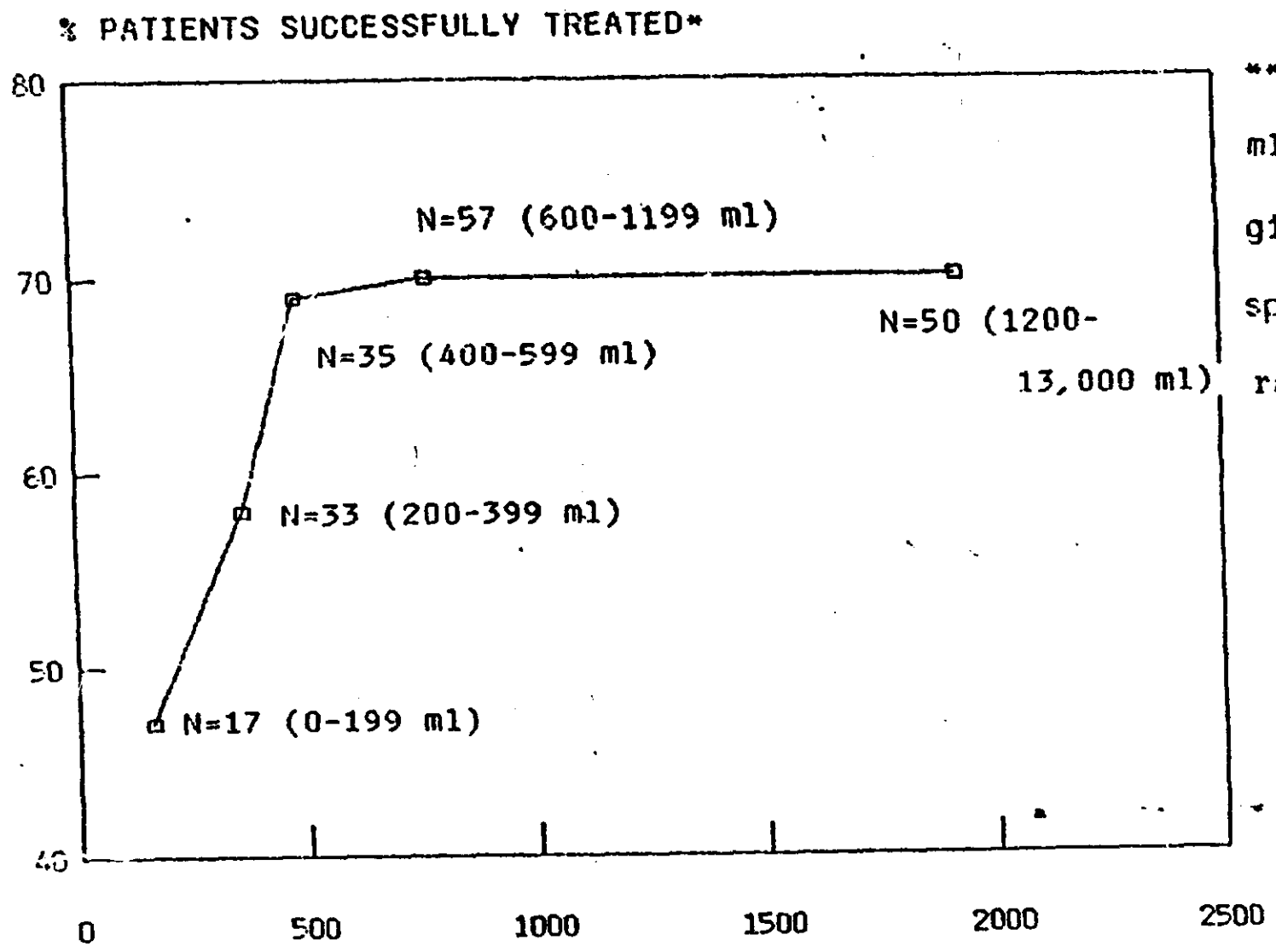
3. Patients in the Failed or Discontinued Cohort From the Multicenter Study that Derived Some Benefit from Monooctanoin Therapy

Success was defined in the multicenter study as either stone disappearance or size reduction. In some patients, however, monooctanoin facilitated the nonsurgical (Dormia basket, balloon catheter, etc) removal of biliary calculi by making them friable and thus more susceptible to extraction with the procedures that were ultimately employed. Twelve of 26 patients that were considered failures on primary monooctanoin therapy were judged by their attending physicians to have derived adjunctive benefit from monooctanoin. If this group of patients were included in the success cohort (complete and partial success combined), the overall percentage with a successful outcome on monooctanoin would be increased from 56% to 60%. This increase may understate the actual number of patients benefiting from adjunctive monooctanoin therapy, since the study protocol did not require that this type of information be recorded.

4. Influence of Monooctanoin Dosage on Clinical Outcome

It can be seen from Figure 5 that, as the dose of monooctanoin increases up to about 500 ml, the proportion of patients with a successful clinical outcome also increases. These data are consistent with the finding that indicates a longer duration of treatment (i.e. more monooctanoin) produces a more desirable clinical effect.

Figure 5. Effect of monooctanoin on stone dissolution in vivo (Humans)



*Within a specified dosage range

** Median, in ml., of Noctanoin given within specified dose range

C. Comparison of Multicenter Results With Other Monooctanoin Experiences

There are a number of other reports in the literature detailing the use of monooctanoin in the treatment of choledocholithiasis. Velasco et al (13) administered monooctanoin for 5 to 10 days to 9 Chilean patients with retained common bile duct (CBD) stones and observed complete disappearance in 7, size reduction in 1, and no change in the final subject. In Germany, Schenk et al (14) infused monooctanoin for a maximum of 10 days in 11 patients with CBD calculi using either a T-Tube or nasobiliary tube (NBT). In 6 of the 11 cases, total or partial dissolution of the calculi occurred eliminating any need for further operative or invasive treatment. The 55 to 89% success rate (complete plus partial) reported in these initial monooctanoin trials has been confirmed by a number of studies conducted in the United States and other countries throughout the World. These include: Great Britain - 83% success (10), Mexico - 58% success (9), West Germany - 77% success (11), Italy - 88% success (8), and the U.S. - 62, 79, 83% (7,15,16) The 127 subjects treated with monooctanoin in the investigations listed above were perfused for an average 11.1 days with 550 ml of dissolving agent. A mean of 81% of these patients benefitted from monooctanoin therapy which is considerably higher than the 61% derived from the analysis of the current multicenter trial data.

Clinical outcome for patients receiving monooctanoin in the multicenter trial is presented in Table 14, and contrasted with five other studies that were reported in the medical literature. In general, the proportion of patients successfully treated with monooctanoin infusion in the published studies (2, 8-11) was somewhat higher than in the multicenter trial (78 vs 54%). This may be attributed to a number of factors. First, the average calculus was larger (13.6 vs 10.7 mm) and the duration of infusion shorter (9.2 vs 12.8 days) for the multicenter group in comparison to the most successful studies that were published in the literature. Indeed, the patients reported by Uribe et al (58% success) (9), were only treated for 5.3 days which suggests that, at least in part, treatment outcome is a function of the length of perfusion with monooctanoin. Secondly, the multicenter data base is relatively heterogeneous (i.e. a large number of physicians contributed a small number of subjects) unlike the published studies in which each group treated a substantial number of patients. This latter circumstance allows for the attainment of

technical proficiency which is undoubtedly an important determinant of clinical outcome in this type of procedure.

Table 14. Clinical outcome for patients receiving monoctanoin for the dissolution of biliary calculi

Study Group*	Location	Study Published	Success**	Failure**	Discontinued**	Total
Multicenter	United States and numerous foreign countries	-	212 (56%)	113 (30%)	52 (14%)	377
J. Thistel †	United States	Gastroenterol. 1980, 79: 1016-1022.	10 (83%)	2 (17%)	-	12
L. Jarrett †	Great Britan	Lancet. 1981, 1:68-70.	20 (83%)	4 (17%)	-	24
L. Witzel †	West Germany	Gastrointest. Endoscopy. 1981, 27: 63-65.	13 (77%)	2 (12%)	2 (12%)	17
M. Tritapepe †	Italy	Am. J. Gastroenterol. 1984, 79: 1-11.	14 (88%)	2 (13%)	-	16
M. Uribe †	Mexico	Digestive Dis. Sci. 1981, 26: 636-640.	7 (58%)	5 (42%)	-	12

* Multicenter study group encompasses all patients included in the NDA submitted by Ascot Pharmaceuticals. † denotes the senior author of a publication on monoctanoin the dissolution of biliary calculi that has appeared in the literature and was described on pages 125-132 of the NDA. With the possible exception of two patients (1 Thistle, 1 Jarret), none of these patients were included in the multicenter analysis.

** Number of patients (% of total in parenthesis) that were treated successfully or unsuccessfully (failure) with monoctanoin were discontinued from the trial. Success defined as stone(s) disappeared, or were reduced in size; Failure: stones neither disappeared nor were reduced in size; Discontinued: patient discontinued for some reason.

D. Comparison of Monooctanoin with Other Treatments of Biliary Calculi:

The use of monooctanoin for the dissolution of biliary calculi has been compared with heparin in a prospective, randomized trial conducted by Velasco and his associates (17). In this study, all patients admitted with retained duct stones and a T-tube in the common duct during a two year period (1978-1980), were randomized to receive infusions of either heparin 25,000 units in 250 ml saline, or monooctanoin 408 ml/h continuously with an infusion pump during the previous year by saline washout. There was no statistically significant difference in the size, number and location of stones in the three groups before the beginning of treatment. Disappearance of stones occurred in 11/54 (20%) in the control group, 5/15 (33%) in the heparin group and 13/20 (65%) in the monooctanoin group, a statistically significantly more effective treatment in the latter than in the previous 2 groups. Six patients in the monooctanoin group required a second infusion for another 5 days; in 4, the stones disappeared and the other two required surgery. The incidence of side effects in patients receiving monooctanoin was abdominal discomfort 75%, diarrhea 65%, vomiting 50%. One patient developed jaundice and chills after 4 days of infusion; klebsiella was identified on blood culture. The patient was treated with antibiotics and made a complete recovery. Subsequent X-ray examination showed no stones. Although other workers have achieved more impressive results with heparin (72% success) (18) the failure of heparin to display a convincing gallstone dissolving capacity in vitro has led to the suggestion that any clinical benefit associated with heparin therapy is due to a simple flushing effect (19, 20). A number of studies have shown that bile acids are efficacious dissolving agents for choledocholithiasis with success rates varying from 33 to 83% in 10 separate series (20). It is also generally accepted that cholic acid, although inferior to monooctanoin, is capable of dissolving cholesterol stones in vitro (1,6).

Surgical removal (choledocholithotomy) is still probably the most commonly employed method for treating retained bile duct stones. It should be emphasized, however, that common duct exploration in the absence of intraoperative choledochoscopy or cholangiography has resulted in stone retrieval in a relatively small percentage of patients (27-53%) (21). Hicken et al (22) has reported that cystic duct cholangiography reduced

the number of negative choledochostomies by 90% in their series involving 1293 subjects. Similarly, Jolly et al were able to recover stones from 78% of those patients having a positive intraoperative cholangiogram (23).

For patients with recurrent ductal calculi, choledochoduodenostomy, subsequent to choledochostomy, has been shown to be associated with less morbidity (8.0 vs 27%), mortality (0 vs 4.4%), and incidence of reoperation (0 vs 21%) than T-tube drainage (24). These findings have been confirmed by Lygidakis (25) who randomly assigned 120 patients with recurrent choledocholithiasis to 3 treatment groups. Group A received the CBD-duodenal anastomosis, group B, sphincteroplasty, and group C, T-tube placement. Group A subjects had low early morbidity (10%), and no mortality or reoperation. In contrast, group B and C has much higher morbidity (25 and 30%), mortality (5 and 2.5%), and reoperation rates (13 and 23%). Andenberg et al (26) also performed choledochoduodenostomy on 20 subjects after surgical removal of CBD stones and observed pneumonia in one patient but no mortality. Eighteen of the 20 subjects were free of postoperative symptoms, while one had recurrent cholangitis due to a stricture in the anastomosis, and the other had multiple intrahepatic retained stones.

For those patients in whom surgery is contraindicated due to age or complicating condition, a number of relatively new procedures for calculus removal have gained widespread acceptance by the medical community. Mazzariello (27) has been able to remove residual stones from 204 of 220 patients through the passage of forceps or a Dormia basket into the T-tube tract under continuous fluoroscopic guidance. The primary cause of treatment failure was complex fistulous (T-tube) tracts (4 cases), calculus impaction in the ampulla of Vater (3 cases), closing of the proximal portion of the T-tube tract (3 cases), and difficulty in reanalyzing the cystic duct (3 cases). Complications included pain and emesis in 16 subjects, cholangitis with fever (9 cases) or jaundice (3 cases), and the accidental creation of a secondary passage in the T-tube tract (4 cases).

Burhenne (28) has also reported on the use of a basket extraction technique through the mature T-tube tract. He analyzed data obtained from 612 subjects who were treated at 38 institutions for retained bile duct stones. Calculi were not extracted in 9% of the patients in this series and necessitated reoperation.

A reoperation was also required in an additional three patients due to (A) the basket engaging a common duct papilloma, (B) a large stone was ensnared by the basket but could not be removed through the sinus tract, and (C) post-extraction drainage of bile collection. No mortality was seen in this study, although morbidity included sinus tract perforation (7 cases), fever (12 cases), subhepatic bile collection (2 cases), sepsis (2 cases), pancreatitis (2 cases), and vasovagal reaction (2 cases).

For those patients diagnosed as having residual stones in the biliary tree but without a mature T-tube tract, endoscopic papillotomy or sphincterotomy (either with or without basket or balloon catheterization) is a viable alternative to surgical intervention. Koch et al (29) and Safrany (30) were among the first to report on their experience with this procedure. Koch et al (29) used endoscopic papillotomy on 267 patients in West Germany, 222 of whom had choledocholithiasis. In this group of 222 patients, calculi passed spontaneously in 108, a basket catheter was required for removal in 84, surgery was needed in 12, and in 18 others stones remained in the CBD. The overall success rate was 87% with the most serious complications being pancreatitis (9 cases), hemorrhage (7 cases, 5 requiring surgery), duodenal perforation (2 cases requiring surgery),and cholangitis (1 case requiring surgery). One of the patients with bleeding died after surgery (3 days), as did a woman with cholangitis (7 days post surgery). Safrany's (30) data is somewhat similar to that reported by Koch et al. In 185 subjects, calculi passed spontaneously after duodenoscopic sphincterotomy in 106, were basket extracted (Dormia) in 67, and retained in 12. Three patients died from therapy (2 cholangitis-septicemia, 1 pancreatitis). Morbidity was observed in 10% of the patients and included 8 cases of retroperitoneal perforation, 7 bleeding, 5 cholangitis, 3 pancreatitis, and 1 subject with an instrument-induced injury.

Since the publication of Koch and Sufrany's studies in 1977, a number of articles have appeared which substantiate their early observations on the utility of endoscopic papillotomy (EP) in the treatment of retained bile duct stones. Novis et al (31) demonstrated spontaneous passage of stones in 44 of 56 patients in Israel that were provided an endoscopic directed sphincterotomy (ES). In three subjects, the sphincterotomy required extension, and in three others the stones were extracted via a Dormia basket. Stones failed to pass in four patients and were surgically

removed. Cholangitis and severe pancreatitis were the only complications noted. In Canada, Passi et al (32) performed EP on 31 patients with stone removal occurring in 26 (84% success). Pancreatitis developed in 4 patients, minor bleeding in one, and acute cholangitis in 2. In a U.S. study, Mazzeo et al (33) showed that calculi were absent in 41 of 51 EP patients with stone retention occurring in the remaining 10. Surgery was required for retained stones in 4 patients, and recommended for CBD calculi in excess of 2.5 cm. Minor complications were reported in this study including 5 episodes of bleeding for an overall morbidity rate of 15.2%. The mortality incidence was 3.4%. In a final study conducted in the United Kingdom, Neoptolemos et al (34) performed endoscopic sphincterotomy on 98 subjects with an intact gallbladder and CBD stones. Stones were completely extracted in 91 of these patients. One patient who presented in extremis died following failed calculus extraction. On follow-up (4-50 months), 16 patients have died but only one from gallbladder sepsis.

The effectiveness of various physical methods (surgery, papillotomy, basket-balloon-forcep extraction, etc.) of treating choledocholithiasis is thus generally superior to the results of dissolution with monooctanoin. In certain clinical circumstances, however, (elderly subject, large stone, multiple stones, etc.) Monooctanoin perfusion may be the method of choice for attempted removal of biliary calculi. It remains possible that ultimately a still smaller population will require this treatment. Reimann et al (35)and Staritz et al (36) have both utilized a mechanical lithotripter to crush large CBD stones. In each study, eight patients were successfully treated with this technique. Orii and his colleagues (37) were also able to remove all or most of the HBD and CBD stones in 11 patients with a Yag laser - choledochofiberscope combination. It remains to be seen, therefore, what the ultimate place in therapy of monooctanoin will be. It's labeling emphasizes, however, that it is to be used when other means have failed or cannot be undertaken.

E. Safety of Monooctanoin in the Treatment of Patients with Biliary Calculi

The side effects accompanying monooctanoin infusion in the multicenter study have been tabulated (Tables 10, 15). Side effects are very common, and the cause of considerable discomfort that can be severe, even life threatening. Briefly, about 3/4 of patients experience some adverse effect: 43% of the patients given

Monooctanoin experienced pain, 32% nausea, 20% emesis, 19% diarrhea, 6% fever, and 18% some other adverse reaction of which discomfort (7%) and anorexia (3%) were the most common (Table 10). In addition, 45 subjects (14%) had to be discontinued from the trial for a variety of reasons, the most prevalent being severe and/or immediate side effects (Table 14).

The incidence of adverse reaction in the multicenter trial is similar to that described in a considerable number of published studies. Of 117 adequately characterized subjects receiving monooctanoin (7-11, 13, 14, 17, 38), 33% had pain or abdominal discomfort, 29% nausea, 28% diarrhea, and 21% emesis, with 6% discontinuations. Eight percent of these subjects were without side effects in contrast to 23% of those in the multicenter study. One patient from this series developed dehydration and hyponatremia secondary to diarrhea (9) and expired 4 days after discontinuing monooctanoin.

In addition to the serious adverse effects described above, there have been other published reports of other serious reactions. Crabtree et al (39) discontinued monooctanoin after 60 hr perfusion in a 72 year old man with radiologically proven CBD stones due to abdominal pain, nausea, and emesis. These symptoms were followed by progressive jaundice, anorexia and fever. This patient was treated with antibiotics, but nevertheless expired 5 weeks after discontinuing the perfusion. Autopsy revealed acute pancreatitis and cholangitis, and a biliary tree filled with pus and a black biliary cast.

Minuk et al (40) administered monooctanoin to a 25 year old woman with numerous intra and extrahepatic stones, and cirrhosis secondary to chronic active lupoid hepatitis. On three separate occasions, monooctanoin infusion at 3-5 ml/hr produced right upper quadrant pain and systemic side effects including facial flushing, metallic taste sensation, and dyspnea, with low arterial blood partial pressure in relation to the degree of hyperventilation. Symptoms resolved promptly on each occasion with monooctanoin discontinuation.

Table 15. Comparison of side effects in U.S. and foreign patients receiving Monooctanoin for dissolution of biliary calculi

Variable	United States	Foreign	Statistics*
Pain	117	22	NSD
Nausea	87	17	NSD
Emesis	51	14	NSD
Diarrhea	50	13	NSD
Fever	18	-	NSD
Other	47	10**	NSD
Total Pt with Side Effects	208	43	NSD
Pt with Multiple Side Effects	113	21	NSD
Pt Without Side Effects	66	9	NSD
Total Pt	274	52	

*Derived from chi-square analysis.
** Other includes: Discomfort (4), fullness (2), intolerance (2), pyrexia (1), itching (1), anorexia (1).

In an attempt to define histopathological alterations occurring in patients receiving monooctanoin, Geenan and his associates (41) obtained serial biopsy specimens from the gastric antrum, duodenum and bile duct of 10 subjects given monooctanoin at 2.5 ml/hr for 7-10 days. A diffuse erythremia was observed in the antral and duodenal mucosa of 3 of 10 and 10 of 10 subjects, respectively. Duodenal erosion was also seen in 6 of 10 patients at both 3 and 7 days post-treatment, while inflammatory cell infiltration was present in 5 of 10 patients. In three of five subjects, ulcerations were manifest in the CBD mucosa. No mucosal abnormalities were seen one month after discontinuing monooctanoin. Four of the subjects in this series experienced pain and nausea, and all had frequent loose stools.

Histopathologic changes accompanying monooctanoin infusion have also been reported by other investigators (8, 14, 38, 42). Schenk et al (14, 38) noted duodenal erosions and localized mucosal inflammation in two of five and two of six patients, respectively. Duodenal edema and/or inflammatory cell infiltration also occurred in four of the seven subjects treated by Triatepep et al (8). Finally, Train et al (42) described a 57 year old man who developed hematemesis on the 11th day of monooctanoin administration (10 ml/hr) which resulted from multiple deep ulcerations in the duodenum adjacent to the top of the ring catheter. These authors concluded that the high rate of monooctanoin infusion in direct contact with the duodenal mucosa was the cause of the ulcerous condition.

VI. Approved Package Insert:

A copy of the package insert is attached.

ascol

MOCTANIN™ (MONOOCTANOIN)

DESCRIPTION: MOCTANIN™ (MONOOCTANOIN) is a semi-synthetic esterified glycerol. The mixed mono-di-glyceride has the following approximate composition:

Glyceryl-1-mono-octanoate	80-85%
Glyceryl-1-mono-decanoate	10-15%
Glyceryl-1-2-di-octanoate	
Free Glycerol	max. 2.5%

with the basic structural formula

CH_2OH

$CH\text{-}OH$

CH_2OOR

MOCTANIN™ is a clear, viscous, sterile liquid intended for perfusion of the common bile duct for cholesterol stone dissolution.

CLINICAL PHARMACOLOGY: Moctanin™ (monooctanoin) has been shown *in vitro*, to have 2-5 times greater dissolution capacity for cholesterol gallstones (about 120 mg cholesterol/ml of Moctanin™) than does sodium cholate.

Moctanin™ is readily hydrolyzed by pancreatic and other digestive lipases. The liberated fatty acids are excreted or absorbed and metabolized in a normal fashion.

Moctanin™ is irritating to the gastrointestinal and biliary tracts in animals and man. The degree of irritation is related to perfusion pressure and rate; both should be carefully monitored. Such irritation was found to be reversible and disappeared 2-7 days after therapy was completed.

In several animal species, perfusions of Moctanin™ into the biliary tract was associated with inflammation of the common bile duct and gastric mucosa. Administration to dogs via a Heidenhain pouch resulted in a disruption of the ionic mucosal barrier, similar to that seen with bile acid reflux. Direct injection of low doses of Moctanin™ into the left hepatic lobe of rat livers produced fibrotic areas with hyalinized, necrotic centers, and at a higher dose, 9 out of 10 rats died of hemorrhagic pneumonitis within 30 minutes of the injection.

In man, biopsies from the gastric antrum, duodenum and bile ducts have shown diffuse erythema in the antral and duodenal mucosa. Ulceration or irritation of the common bile duct mucosa has also been observed on endoscopic examination. Duodenal erosion, inflammatory cell infiltration and localized inflamation have been reported. In one patient, multiple duodenal ulcerations adjacent to the infusion catheter were observed. No mucosal abnormalities were seen one month after discontinuation of therapy.

INDICATIONS AND USAGE: Moctanin™ is indicated as a solubilizing agent for cholesterol (radiolucent) gallstones retained in the biliary tract following cholecystectomy, when other means of removing cholesterol stones retained in the common bile duct have failed or cannot be undertaken.

Treatment results in complete stone dissolution about one-third of the time and in reduction in stone size in approximately another one-third of patients. When reduced in size these stones may pass spontaneously or may be more susceptible to physical extraction. Complete dissolution is much more likely when there is a single stone (almost 50%) than when there are multiple stones (about 20%). For unclear reasons, complete dissolution is uncommon in diabetic patients (about 10%).

CONTRAINDICATIONS: Moctanin™ *should not* be used in patients with clinical jaundice, significant biliary tract *infection* or with a history of recent duodenal ulcer or jejunitis.

WARNINGS: MOCTANIN™ IS INTENDED FOR BILIARY TRACT PERFUSION ONLY AND IS NOT FOR PARENTERAL USE.

Pressure of the infusion should be kept below 15cm of H_2O. (See Dosage and Administration.)

Moctanin™ has been *shown to be irritating* to the gastrointestinal and biliary tracts of *animals and humans*. The irritation seems closely related to perfusion *pressure and rate of* administration; both should be closely monitored. (*See Dosage and* Administration.) Ascending cholangitis has been *reported with* Moctanin™ therapy, possibly related to some form of *obstruction in the common* bile duct. If fever, anorexia, chills, leucocytosis, severe *right upper quadrant* abdominal pain or jaundice occur, *discontinue treatment*.

PRECAUTIONS

General: Moctanin™ (monooctanoin) *should only be* administered by individuals experienced in *perfusion therapy*.

Patients should have routine liver function tests since those with impaired function may *experience* metabolic acidosis during MOCTANIN™ infusion.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *No data available.*

PREGNANCY: TERATOGENIC EFFECTS

Pregnancy Category C. Animal reproduction studies *have not been* conducted with MOCTANIN™. It is also not known whether MOCTANIN™ can cause fetal harm when administered to a *pregnant woman* or can affect reproduction capacity.

MOCTANIN™ *should be given* to a pregnant woman only if clearly needed.

NURSING MOTHERS: *It is not known* whether this drug is excreted in human milk. *Because many drugs are* excreted in human milk, caution should be exercised *when* MOCTANIN™ is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children *have not* been established.

ADVERSE REACTIONS: Abdominal pain or distress and nausea and/or *vomiting were* the most common side effects reported by patients *receiving* MOCTANIN™ therapy.

The a*dverse reactions incidences* listed in the following tables are based on observations of 326 *patients* (274 U.S. and 52 foreign) treated with Moctanin™. The *reactions are arranged* in order of decreasing frequency.

Irritation of the duodenal mucosa during perfusion has been observed by endoscopy. This was found to be reversible and disappeared 2-7 days after MOCTANIN™ therapy was completed.

ADVERSE REACTIONS OCCURRING IN MORE THAN 1% of MOCTANIN™ TREATED PATIENTS

N=326

Reaction	No. of Reactions	Frequency (%)
Gastrointestinal Pain	139	43
Nausea	104	32
Emesis	65	20
Diarrhea	63	19
Discomfort	24	7.3
Fever	19	6.3
Anorexia	10	3.0
Loose Stool	5	1.5
Indigestion	4	1.2

ADVERSE REACTIONS OCCURRING IN LESS THAN 1% OF MOCTANIN™ TREATED PATIENTS

N=326

Reaction	No. of Reactions	Frequency (%)
Gastrointestinal		
Burning Epigastrium	1	0.3
Increased Drainage from Fistula	1	0.3
Hepatic		
Increased Serum Amylase	2	0.6
Bile Shock	1	0.3
Hematological		
Persistent Leucopenia	1	0.3
Electrolyte		
Hypokalemia	1	0.3
Other		
Intolerance	2	0.6
Pruritus	3	0.9
Chills	1	0.3
Fatigue/Lethargy	3	0.9
Depression	1	0.3
Diaphoresis	1	0.3
Headache	1	0.3
Allergic Reaction	1	0.3

The following table identifies those reactions which were considered severe enough to discontinue therapy. The most common side effects were pain, nausea, emesis, diarrhea, and fever.

REASONS FOR PATIENT DISCONTINUATION

N=326

Reason	Number of Patients
Severe and/or immediate side effects.	25
Pt. refused further Rx.	4
No reason given.	2
Stone impacted, obstructive jaundice.	2
Bile shock, diaphoresis	1
Allergic reaction.	1
Pressure > 15cm	1
Liver function enzymes elevated.	1
Pt. had cerebrovascular accident.	1
Pt. with sepsis, CHF, and renal failure died after 24 hr perfusion.	1

Overall, 251 (77%) of the MOCTANIN™ treated patients had side effects; 134 (41%) had multiple side effects. Most of these were mild gastrointestinal symptoms. Some were tolerated, some abated with reduced perfusion rate and discontinuation during meals. Side effects and other events caused discontinuation in 41 (12.5%) of the 326 patients.

Also reported in the literature was one death apparently due to acute pancreatitis and cholangitis, and one patient with hematemesis from multiple duodenal ulcerations. A patient with lupus erythematosus developed upper right quadrant abdominal pain, dyspnea and hypotension with hyperventilation. The symptoms abated when the drug administration was discontinued.

DOSAGE AND ADMINISTRATION: MOCTANIN™ (MONOOCTANOIN) is administered as a continuous perfusion through a catheter inserted directly into the common bile duct generally via a T-tube or through a naso biliary tube placed by endoscopy.

IT IS ESSENTIAL TO HAVE AN OVERFLOW MANOMETER, PERISTALTIC PUMP OR SIMILAR MEANS TO ASSURE THAT PERFUSION PRESSURE DOES NOT EXCEED 15 cm H_2O.

Perfusion should be at a rate of not more than 3.0 to 5.0 ml/hour at a pressure of 10 cm H_2O to minimize gastrointestinal and/or biliary tract irritation. Administration may be interrupted during meals.

Perfusion is best regulated by a Peristaltic Infusion pump. Out patients have used battery operated portable pumps.

MOCTANIN™ must not be administered intravenously or intramuscularly.

MOCTANIN™ should be warmed to 60-80°F prior to being perfused and care should be taken that the temperature of the perfusate does not fall below 65°F during administration.

Stones must be radiolucent and readily accessible to the perfusate. If recently removed stones are available they should be analyzed for composition or incubated in MOCTANIN™ at body temperature with stirring. If analysis shows the stone to be other than cholesterol or if no dissolution is observed after *72 hours* incubation, MOCTANIN™ therapy should not be instituted.

Duration of perfusion of MOCTANIN™ is from 7 to 21 days. If, after 10 days, endoscopy or x-ray shows neither elimination nor reduction in size of stones therapy should be discontinued.

HOW SUPPLIED: MOCTANIN™ (NDC 47879-399-18) is supplied in glass bottles containing 120 ml of sterile liquid, ready for use, with disposable bottle hanger. Store at controlled room temperature (59-86°F) 15-30° C

Distributed by: Ascot Pharmaceuticals, Inc.
Skokie, Illinois 60077

Rev. 11/85

VII. BIBLIOGRAPHY

1. Thistle, J.L., Carlson, G.L., Hofmann, A.F., Babayan, V.K.: Medium Chain Glycerides Rapidly Dissolve Cholesterol Gallstones in Vitro. Gastroenterology. 72: 1141, 1977.

2. Thistle, J.L., Carlson, G.L., Hofmann, A.F., LaRusso, N.F., Mac Carthy, R.L., Flynn, G.L., Higuchi, W.I., Babayan, V.K.: Monooctanoin, a Dissolution Agent for Retained Cholesterol Bile Duct Stones: Physical Properties and Clinical Application. Gastroenterology. 78: 1016-1022, 1980.

3. Gadacz, T.R.: Efficacy of Capmul and the Dissolution of Biliary Stones. J. Surg. Res. 26: 378-380, 1979.

4. Antezana, C., Csendes, A.: In Vitro Dissolution of Cholesterol Gallstones with Sodium Cholate, Heparin and Monooctanoin. Rev. Med. Chile. 109: 601-605, 1981.

5. Sharp, K.W., Gadacz, T.R.: Selection of Patients for Dissolution of Retained Common Duct Stones with Mono-octanoin. Ann. Surg. 196 (2): 137-139, 1982.

6. Teplick, S.K., Pavlides, C.A., Goodman, L.R., Babayan, V.K.: In Vitro Dissolution of Gallstones: Comparison of Monooctanoin, Sodium Dehydrocholate, Heparin and Saline. Am. J. Roentgenal. 138: 271-273, 1982.

7. Venu, R.P., Geenan, J.E., Toouli, J., Hogan, W.J., Kozlov, N., Stewart, E.T.: Gallstone Dissolution Using Mono-Octanoin Infusion through an Endoscopically Placed Nasobiliary Catheter. Am. J. Gastroenterol. 77: 227-230, 1982.

8. Tritapepe, R., Di Padova, C., Pozzoli, M., Rovagnati, P., Montorsi, W.: The Treatment of Retained Biliary Stones with Monooctanoin: Report of 16 Patients. Am. J. Gastroenterol. 79 (9): 1984.

9. Uribe, M., Uscanga, L., Farca, S., Sanjurjo,L., Lagarriga, J., Ortiz, J.H.: Dissolution of Cholesterol Ductal Stones in the Biliary Tree with Medium-Chain Glycerides. Dig. Dis. Sci. 26 (7): 636-640, 1981.

10. Jarrett, L.N., Balfour, T.W., Bell, G.D., Knapp, D.R.: Intraductal Infusion of Monooctanoin: Experience in 24 Patients with Retained Common-Duct Stones. The Lancet. January: 68-70, 1981.

11. Witzel, L., Wiederholt, J., Wolbergs, E.: Dissolution of Retained Duct Stones by Perfusion with Monooctanoin Via a Teflon Catheter Introduced Endoscopically. Gastrointestinal Endoscopy. 27 (2): 63-65, 1981.

12. Fleiss, J.L.: Statistical Methods for Rates and Proportions. John Wiley & Sons. 223pp, 1973.

13. Velasco, N., Csendes, A.: Treatment of Retained Common Duct Stones with Intraductal Infusion of Monooctanoin. Rev. Med. Chile. 108: 1021-1023, 1980.

14. Schenk, J., Schmack, B., Rosch, W., Riemann, J.F., Koch, H., Demling, L.: Irrigation Treatment of Concrements in the Common Bile Duct With Octanoate (Capmul 8210). Deutsche Medizinnische Wochenschrift. 105: 917-921, 1980.

15. Gadacz, T.R.: The Effect of Monooctanoin on Retained Common Duct Stones. Surgery. 89 (5): 527-531, 1981.

16. Mack, E., Patzer, E.M., Crummy, A.B., Hofmann, A.F., Babayan, V.K.: Retained Biliary Tract Stones: Nonsurgical Treatment with Capmul 8210, a New Cholesterol Gallstone Dissolution Agent. Arch. Surg. 116: 341-344, 1981.

17. Velasco, N., Braghetto, I., Csendes, A.: Treatment of Retained Common Bile Duct Stones: A Prospective Controlled Study Comparing Monooctanoin and Heparin. World J. Surg. 7: 266-270, 1983.

18. Gardner, B., Dennis, C.R., Patti, J.: Current Status of Heparin Dissolution of Gallstones. Am. J. Surg. 130: 293, 1975.

19. Allen, B.L., Deveney, C.W., Way, L.W.: Chemical Dissolution of Bile Duct Stones. World J. Surg. 2: 429-437, 1978.

20. Motson, R.W.: Dissolution of Common Bile Duct Stones. Brit. J. Surg. 68 (3): 203-208, 1981.

21. Birkett, D.H., Williams, L.F.: Prevention and Management of Retained Bile Duct Stones. Surgical Clinics of North America. 61 (4): 939-950, 1981.

22. Hicken, N.F., McAllister, A.J.: Operative Cholangiography as an Aid in Reducing the Incidence of "Overlooked" Common Bile Duct Stones: A Study of 1,293 Choledocholithotomies. Surgery. 55: 753-758, 1964.

23. Jolly, P.V., Baker, J.W., Schmidt, H.M., et al: Operative Cholangiography: A Case For Its Routine Use. Ann. Surg. 168: 551-565, 1968.

24. Lygidakis, N.J.: Surgical Approaches to Recurrent Choledocholithiasis. Choledochoduodenostomy Versus T-tube Drainage After Choledochotomy. Am. J. Surg. 145 (5): 636-639, 1983.

25. Lygidakis, N.J.: A Prospective Randomized Study of Recurrent Choledocholithiasis. Surg. Gynecol. Obstet 155 (5): 679-84, 1982.

26. Anderberg, B., Bolin, S., Heuman, R., Sjodahl, R.: Choledochoduodenostomy For Choledocholithiasis. Indications and Functional Results. Acta. Chir. Scand. 150 (1): 75-78, 1984.

27. Mazzariello, R.: Review of 220 Cases of Residual Biliary Tract Calculi Treated Without Reoperation: An Eight-Year Study. Surgery. 73: 299-306, 1973.

28. Burhenne, H.J.: Complications of Nonoperative Extraction of Retained Common Duct Stones. Am. J. Surg. 131: 260-262, 1976.

29. Koch, H., Rosch, W., Schaffner, O., et al: Endoscopic Papillotomy. Gastroenterol. 73: 1393-1396, 1977.

30. Safrany, L.: Duodenoscopic Sphincterotomy and Gallstone Removal. Gastroenterol. 72: 338-343, 1977.

31. Novis, B.H., Pomeranz, I.: Endoscopic Sphincterotomy in Biliary Tract Disease. Isr. J. Med. Sci. 18 (5): 619-623, 1982.

32. Passi, R.B., Raval, B.: Endoscopic Papillotomy. Surgery. 92 (4): 581-588, 1982.

33. Mazzeo, R.J., Jordan, F.T., Strasius, S.R.: Endoscopic Papillotomy for Recurrent Common Bile Duct Stones and Papillary Stenosis. A Community Hospital Experience. Arch. Surg. 118 (6): 693-695, 1983.

34. Neoptolemos, J.P., Carr-Loche, D.L., Fraser, I., Fossard, D.P.: The Management of Common Bile Duct Calculi by Endoscopic Sphincterotomy in Patients with Gallbladders in Situ. Br. J. Surg. 71 (1): 69-71, 1984.

35. Riemann, J.F., Sueberth, K., Demling, L.: Clinical Application of a New Mechanical Lithotripter for Smashing Common Bile Duct Stones. Endoscopy, 14 (6): 226-230, 1982.

36. Startiz, M., Ewe, K., Meyer-zum-Buschenfelde, K.H.: Mechanical Gallstone Lithotripsy in the Common Bile Duct--In-Vitro and In-vivo Experience. Endoscopy. 15 (5): 316-318, 1983.

37. Orii, K., Ozaki, A., Takase, Y., Iwasaki, Y.: Lithotomy of Intrahepatic and Choledochal Stones With Yag Laser. Surg. Gynecol. Obstet. 156 (4): 485-488, 1983.

38. Schenk, J., Schmack, B., Riemann, J.F., Rosch, W: Treatment of Choledocholithiasis Using the Transpapillary Perfusion Technique Endoscopy. 12 (5): 224-227, 1980.

39. Crabtree, T.S., Dykstra, R., Kelly, J., Preshaw, R.M.: Necrotizing Choledochomalacia After Use of Monooctanoin to Dissolve Bile-Duct Stones. Can. J. Surg. 25 (6): 644-646, 1982.

40. Minuk, G.Y., Hoofangle, J.H., Jones, E.A.: Systemic Side Effects from the Intrabiliary Infusion of Monooctanoin for the Dissolution of Gallstones. J. Clin. Gastroenterol. 4: 133-135, 1982.

41. Venu, R.P., Geenen, J.E., Hogan, W.J., Komorwski, R., Johnson, G.K.: A Prospective Study of the Endoscopic and Histologic Effects of Mono-Octanoin Infusion for CBD Stone Dissolution on Upper G.I. and Biliary Tract Mucosa. Am. Society for Gastrointestinal Endoscopy. 1984.

42. Train, J.S., Dan, S.J., Cohen, L.B., Mitty, H.A.: Duodenal Ulceration Associated with Monooctanoin Infusion. Am. J. Roentgenol. 141: 557-558, 1983.

43. Mack, E.A., Saito, C., Goldfarb, S., Crummy, A.B., Thistle, J.L., Carlson, G.L., Babayan, V.K., Hofmann, A.F.: A New Agent for Gallstone Dissolution: Experimental and Clinical Evaluation. Surgical Forum. XXIX: 439, 1978.

44. Schenk, J., Koch, H., Stolte, M., Schmack, B.: Tissue Compatibility of the Gallstone Solubilizer Capmul 8210 - A Study in Cats. Gastroenterology. 76: 1237, 1979.

45. Sharp, K.W., Gadacz, T.R., Sampliner, R.E.: Hepatic Response to Parenchymal Injection of Sodium Cholate and Monooctanoin. American College of Surgeons. XXXII: 176-177, 1981.

46. Lillemoe, K.D., Gadacz, T.R., Weichbrod, R.H., Harmon, J.W.: Effect of Monooctanoin on Canine Gastric Mucosa. Surg. Gynecol. Obstet. 155 (1): 13-16, 1982.

MEDR

Monooctanoin, under the trade name Capmul, was made available for investigative use by Stokely Van Camp, Inc., in 1975. In 1977, Dr. Alan Hofmann, Director of Research in the Division of Gastroenterology at the University of California, San Diego, received IND 13,615 for investigation of Capmul. In 1982 he undertook the monitoring of the use of this product under his IND by physicians requesting its use for attempts to dissolve CBD. In March, 1984, Dr. Hoffman sent a status report of the investigations on Capmul to Dr. Temple (Attachment A).

In September 1982, Dr. Marion Finkel, Director, Orphan Products Development, on the basis of her detailed review of the literature, concluded that monooctanoin was an appropriate candidate for orphan drug status. Accordingly, a Federal Register notice published December 10, 1982 invited submission of a New Drug Application for the use of monooctanoin in dissolving cholesterol gallstones retained after cholecystectomy. In response to this notice, Ascot Pharmaceuticals met with Dr. Finkel to discuss the requirements of an NDA. The present submission, under the trade name Moctan, is a result of that meeting. Although the product is identified chemically as monooctanoin, Moctan contains about 70% of the 1-mono-ester of octanoic acid and about 30% of the di-ester. Physically, it is an oil, and in vitro 100 ml dissolves 12 g of cholesterol. Theoretically then, it should be an excellent solvent for cholesterol gallstones in the biliary tract if it can be brought into intimate contact with the stones for a sufficient period of time.

II CLINICAL STUDIES

A. Published Literature: In her memo of September 1982, Dr. Finkel reviewed the reports of clinical trials of monooctanoin published throught 1981 (Attachment B). I have added reviews of 7 reports which have been published since that time.

Results published in the literature support the claim that infusion of monooctanoin into the biliary tract is effective in dissolution of cholesterol stones either to the point of disappearance or to the point of sufficient reduction in size to make possible successful extraction of the stones by endoscopy. The treatment is attended with a high incidence of adverse effects, primarily abdominal pain, nausea/vomiting and diarrhea but these are in almost all cases manageable by reducing the rate of infusion; in those cases where they are not, discontinuation of the infusion is followed by resolution of the symptoms.

B. Present Submission: The data in this NDA are based on individual case reports on a total of 403 patients treated between May 17, 1975 and October 5, 1983 by a total of 221 investigators, 199 from the United States and Canada, and 22 from 13 other countries. Sufficient information was available on 273 U.S. and 52 foreign subjects to be useful in statistical analyses of the relationship between pretreatment or treatment variables and clinical outcome. Twenty-six patients were not included in any of the analyses for justifable reasons. The sponsor chooses to divide the patients into 2 groups, those treated in the United States or Canada, and those treated in some other country (foreign patients).

C. Procedure

1. Inclusions: Patients with retained cholesterol stones in the common bile duct and direct access to the bile duct by T-tube, percutaneous transhepatic catheter, nasobiliary tube or cholecystostomy catheter.

2. Exclusions: Patients with a grossly infected biliary tree or with parenchymal liver disease.

3. Method of Administration: Monooctanoin, warmed to body temperature, was infused through a T-tube, nasobiliary tube, percutaneous transhepatic catheter or cholecystostomy tube by gravity or by a constant infusion pump. A central venous pressure manometer interposed in the tubing between the pump and the patient was adjusted to prevent a pressure in excess of 12 ml of the oil. The initial infusion rate was 1-2 ml/hr, usually increased to 5 ml/hr, with a maximum rate of 10 ml/hr. Cholangiograms were obtained before and at least at weekly intervals during the treatment period. Routine liver tests were monitored in most subjects. In actual practice, the technique of infusion varied considerably from one investigator to another, especially during the early stages of the investigation.

4. Definition of outcome

a. Complete success. Complete disappearance of the stone(s) during the course of infusion.

b. Partial Success: Stones retained, but some either disappeared or were reduced in size.

c. Failure: Neither disappearance or reduction in size of stones.

d. Discontinued: Neither disappearance nor reduction in size of stones, and the patient and/or physician elected to discontinue treatment.

The latter two groups were considered treatment failures but were kept separate for each of the statistical analyses. "Partial success" was considered a not unfavorable result in that reduction of size of stones might facilitate their subsequent passage or extracton and thus obviate the need for any other intervention; this definition could be defended only if it could be shown that attempts to extract the stones were unsuccessful before infusion, successful after infusion. The data submitted do not document the incidence of such occurrences. According to the sponsor's table 15 (attachment C) follow-up information was available in 60/84 cases of "partial success." Post-infusion elimination of the stones short of surgery was accomplished in 17 cases by basket, 3 by balloon, 6 by multiple procedures, 6 by "others"; in 3 additional cases the stones disappeared on further observation. That these 35/60 successes were a result of reduction in the size of stones by monoctanoin perfusion

III Safety

A. Symptoms: Monooctanoin is attended with a high incidence of adverse reactions (Table 4) as tabulated both by the sponsor and independently by Dr. Hofmann. The most frequent adverse effects were abdominal pain, nausea, vomiting, diarrhea, discomfort and fever. The latter could probably be ascribed to ascending cholangitis associated with CBD obstruction by impacted calculi. According to Dr. Hofmann's analysis severe side effects occurred in 5% of the patients; in at least that number, this was a reason for discontinuing therapy. However, the adverse effects were, with rare exceptions, completely reversible, by reducing the rate of infusion or, when this was not effective, by discontinuing the treatment.

B. Laboratory Parameters: Increase of alkaline phosphatase and SGOT over the baseline (which was often elevated) occurred in 14% and 12% of the patients respectively. The underlying stone disease or a too-high perfusion pressure could be contributing factors to these enzyme elevations. Disturbance of other laboratory parameters was rare.

C. Tissue Injury by Monoooctanoin: At the annual meeting of American Society for Gastrointestinal Endoscopy in May 1984, Venu et al submitted an abstract reporting their findings of the effect of monooctanoin infusion on the upper gastrointestinal mucosa and the bile duct (Venu RP Geenen JE, Hogan WJ, Komorowski R, Johnson JK. A prospective study of the endoscopic and histologic effects of monooctanoin infusion for CBD stone dissolution on upper GI and biliary tract mucosa). At the time of this writing the full report had not been published. Ten patients with large CBD stones were studied by serial endoscopic observation and mucosal biopsy prior to, during and after treatment by monooctanoin infusion. Gross endoscopic appearance was recorded and mucosal biopsies were obtained from the gastric antrum, the ducdenum and the bile duct during endoscopic retrograde cholangiopancreatography and sphincterotomy. A nasobiliary catheter was then inserted into the CBD and monooctanoin 2-5 ml/hr was infused for 7-10 days. Repeat endoscopy and biopsy were performed at 3 and 7 days. In 5 patients the same studies were repeated one month following treatment. Endoscopic examination disclosed diffuse erythema of the antral mucosa (3/10 patients) and duodenum (10/10 patients) plus mucosal erosions of the duodenum (6/10 patients) at both 3 and 7 days. There was no significant histological alteration in the gastric mucosa but significant inflammatory cell infiltration was observed in the duodenum in 5/10 patients; the CBD mucosa showed ulceration in 3/5 patients. No mucosal alterations were observed by either endoscopy or biopsy one month after the infusions. All the patients experienced frequent loose stools and 4/10 experienced epigastric pain and nausea; these symptoms subsided when the infusion was completed. An anatomical basis for the principal adverse effects in the human was thus established, confirming the results of experiments in dogs.

PHARM

NDA 19-368 Moctan

March 5, 1985
Ascot Pharmaceuticals

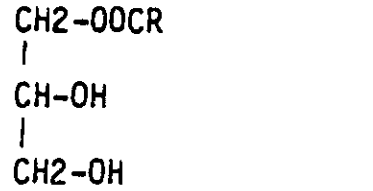
Pharmacology Review

1. Name of Drug: Moctan, Capmul 8210, monooctanoate, monooctanoin.

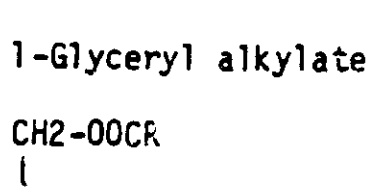
2. Category: Solubilizing Agent for cholesterol gallstones retained in the biliary tract of patients following cholecystectomy; a semi-synthetic esterified glycerol.

3. Chemical Structures:

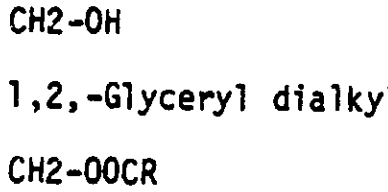
Moctan is prepared by the direct esterification of glycerol with caprylic and capric acids. The products formed are water and the following:



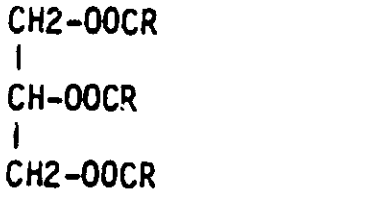
1-Glyceryl alkylate



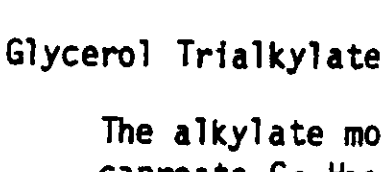
2-Glyceryl alkylate



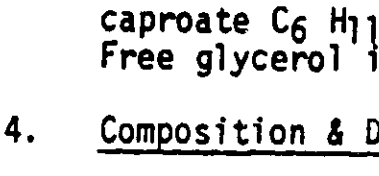
1,2,-Glyceryl dialkylate



1,3,-Glyceryl dialkylate



Glycerol Trialkylate



free Glycerol

The alkylate moiety RCO- is predominantly $C_8 H_{15} O_2$ (80%), caproate $C_6 H_{11} O_2$ (3%) and laurate $C_{12} H_{23} O_2$ (1%). Free glycerol is present at a concentration of about 2.5%.

4. Composition & Dosage Form.

Moctan is a clear, viscuous, sterile liquid supplied in glass bottles containing 120 ml.

5. Dosage, Route & Indication.

Moctan is intended for dissolution of cholesterol gallstones retained in the biliary tract of patients following cholecystectomy. It is administered as a continuous perfusion through a T-tube inserted directly into the common bile duct or through a naso-biliary tube placed by endoscopy.

Perfusion should be at a rate of 3.0 to 5.0 ml/hr at a pressure of 10 cm H_2O; pressure is not to exceed 15 cm H_2O. Moctan should be at 60-80^{0}F. Duration of infusion is 7-21 days.

6. Submitted Preclinical Studies:

A) In Vitro: Considerable in vitro data are supplied which clearly demonstrate the cholesterol solubilizing properties of Moctan. In just several days of standing in Moctan, cholesterol stones are significantly reduced in size or completely dissolved. In contrast, sodium cholate is 1/2 to 1/3 as effective and saline is totally ineffective. Moctan is not very effective against bilirubin stones, but even here slight dissolution occurs which is not seen with other agents tested.

B) In Vivo

Moctan (M, vs. saline in dogs (T.R. Gadasz__ M.D.):

Two cholysystectomized mongrel dogs were infused continuously for 5 days into the common bile duct with 1 ml per hr. (1/5 the maximal clinical rate) of M; another two were similarly infused but sacrificed 14 days after cessation of the infusion. Four cholysystectomized controls were given saline & one was simply sham operated. Tissues examined histologically at term included the distal part of the common bile duct, the antral area of the stomach immediately proximal to the pylorus, the duodenum distal to the entrance of the common bile duct at the Ampulla of Vater, a random section of the liver, and a proximal or mid-portion of the pancreas. Hepatic and pancreatic enzymes were analzed at time of operation, beginning of infusion and at end of infusion.

Results:

The sham operated dog showed no clinical chemistry disturbances. None of four saline treated dogs showed clinical chemistry disturbances related to the infusion. None of the M treated dogs showed serum amylase changes but two of the four dogs showed liver enzyme elevations that may have been related to infusion; one of these dogs (#5) showed slight elevation of SGOT and alkaline phosphatase at the end of infusion that was not apparent before the infusion and the other dog (#4) showed marked elevations of SGPT and alk. phos and moderate elevations of SGOT & serum bilirubin during infusion that had essentially disappeared 14 days after infusion (pre-infusion values are not known-this dog showed foci of hepatic necrosis histologically).

Grossly, it is reported there were no significant changes in the common bile duct, stomach duodenum, liver, or pancreas. No ulceration, erosion, erythema, friability, or stricture was visibly evident in any of the bile ducts.

Histologic exam did not reveal pathological changes in the pancreas, duodenum, or stomach of M treated days. The M treated dog that showed mild liver enzyme change showed mild hepatic congestion & the dog which showed marked enzyme changes showed focal areas of hepatic necrosis. Whereas the common bile duct of saline treated dogs showed only mononuclear cell infiltration, that of the M treated dogs also showed proliferation of the mucosa (3/4) and inflammation (some fibrosis) of at least a mild sort (2/4). The diameter of the common bile ducts of all animals was comparable (avg 6 mm) except for one M treated dog (12 mm).

2. Subacute infusion of M in monkeys ACS Surgical Forum, 1978, 29; 439.

Five monkeys were infused through a T-Tube into the common bile duct (CBD) with M for up to a month and a half at 2.6 ml/hr (half the maximum clinical rate).

Results:

M was said to cause mild to moderate inflammation of the CBD in 4/5 monkeys, but no pancreatitis, diarrhea or deaths.

3. Acute & short-term infusion of M in cats for a short period up to 3/5 the max. clinical rate. Gastroenterology 1979, 76: 1237) The abstract reads as follows-

"TISSUE COMPATIBILITY OF THE GALLSTONE SOLUBILIZER CAPMUL 8210- A STUDY IN CATS". J Schenk, H Koch, M Stolte, B Schmack. Medical and Pathological Department of the University, D-8520 Erlangen, W-Germany.

"The commercial emulsifier Capmul 8210 (a mixture of octanoin-glycerides with glyceryl-mono-octanoate as predominant lipid) is described as an effective agent for dissolving cholesterol gallstones. While its systemic non-toxicity is well known also for man, no data exist about its local tissue compatibility when instilled directly into the biliary tract. METHOD: 17 adult cats wheighing 1,7 - 2,8 kg were anesthetized with pentobarbital sodium (30 mg/kg i.p.). After median laparotomy a teflon tube was inserted to the gallbladder . Capmul was infused via catheter either continuously at a rate of 3 ml/hr for 4/6/8 hours once (group a, n=10) or intermittently for 4 hours daily over a period of 4 days at a rate of 0,6 ml/hr (group B, n=5). In eacn group 1 animal was perfused with 0,9 % NaCl for control. The animals were killed immediately after treatment, and liver, pancreas, gallbladder, common bile duct, and Vater's papilla were examined histopathologically in serial sections. RESULTS: Depending on the contact time, inflammatory epithelial damage like acute oedematous destruction of the biliary and papillary mucosa (group A) or cellular infiltration of the submucous layer as well as acute pancreatitis in 2 cases (group B), were found in the animals treated with Capmul, while no pathological findings were noted in the controls. CONCLUSION: Cholangitis, papillitis, and possibly acute pancreatitis due to repeated contact with Capmul as seen in our animal model-has to be taken into account when choosing this mode of treatment in patients with common bile duct stones."

4. Injection of 0.1 ml of Capmul (Moctan) into left hepatic lobe of adult rats (Sharp et al, ACS Surgical Form, 1981, 32: 176-177):

It is reported that Capmul, sodium cholate, or saline induced the appearance of necrotic, hyalinized centers surrounded by fibrosis in the livers of 6/10, 17/17 and 0/8 animals respectively and that "9 of 10 Capmul treated rats died from hemorrhagic pneumonitis within 30 min of injection." None of the sodium cholate or saline treated rats died.

5. Infusion of Capmul into Heidenhain gastric pouches of dogs (Lillimoe etal, Sury. Gym. Obstet., 1982, 155: 13-16):

Infusion of capmul into the Heidenhain pouches of 6 Mongrel dogs caused disruption of the gastric mucosal barrier as evidenced by dose related increased net hydrogen ion flux and dose related loss of electronegativity of transmucosal electrical potential difference. Similar injury to the gastric mucosa has been observed with bile acids (after kepatitis, the most common lesion in animals treated orally with chenodeoxycholic acid is G.I. irritation and ulceration).

EVALUATION

Moctan is a semi-synthetic mixture of medium chain glycerides formed from the reaction of glycerol with medium chain fatty acids derived from coconut oil. The medium chain fatty acids are predominantly caprylic acid and capric acid.

Moctan is either identical or very similar to an approved GRAS nutritional supplement (MCT) manufactured by Mead Johnson. When Moctan enters the intestinal tract from the perfused biliary tract, it is hydrolized by the pancreatic and intestinal lipases present, mainly to glycerol , caprylic acid and capric acid. These are the same digestion products of the approved food supplement. Also they are no doubt formed in the intestinal tract of any person who consumes coconut or coconut juice. The glycerol and medium chain fatty acids released in the digestion of Moctan are absorbed, metabolized, & excreted just as the digestion products of ordinary coconut or of the approved food supplement.

The preclinical studies submitted on Moctan are limited, but nonetheless they clearly demonstrate two properties: that Moctan solubilizes cholesterol gallstones in vitro and that it is locally irritating to tissue.

Numerous in vitro tests showed that Moctan completely dissolves or significantly reduces the size of cholesterol stones in just a few days. In this respect, it is significantly more effective than sodium cholate or heparin, two other cholesterol solubilizing agents. Moctan is much less effective against bilirubin stones vs chlesterol stones.

The animal toxicity studies which more-or-less reproduced the clinical mode of use showed local irritation as the only apparent outstanding adverse effect. Because the rate of perfusion of the biliary tract in these studies was less than the maximum recommended clinical rate and the duration usually less then the maximum recommended clinical duration, one cannot predict too well how irritating Moctan may prove to be clinically.

However, this reviewer is left with the impression that perfusion in man will most assuredly be accompanied with at least mild irritation in the common bile duct and, on rare instances, perhaps even pancreatitis or hepatitis following rupture of the duct or retrograde diffusion to the liver or pancreas.

The submitted animal data tell us very little about systemic effects (general necropsy or histopathology was not done and there are no LD50 data and no reproduction studies). This perhaps can be excused on grounds that Moctan is intimately related to a food (coconut) and to a GRAS food supplement (MCT) and it is an orphan drug of apparent significant value in a serious medical complication. But, judged from the fact that 9/10 rats died from hemorrhagic preumonitis in 30 minutes from only 1.0 ml (ca 0.5 ml/kg) into the left hepatic lobe suggests that the potential for serious systemic effects is real if administered in a way that allows direct availability to the circulation.

LABELING: The draft package insert is deficient in that it contains no mention of the animal studies and the local irritation observed therein. It should briefly mention that on the basis of these studies local irritation of at least a mild degree can be expected to routinely accompany perfusion and that pancreatitis & hepatitis might conceivably be rare complications. This information might best be inserted at the end of the section headed "Adverse Reactions." The labeling might also recommend routine assessment of serum amylase & warn against accidental parenteral administration (which would most likely cause severe systemic effects). Labeling is further deficient in that a statement noting the absence of any data or the potental for carcinogencity, mutagenicity or impairment of fertility has not been included.

Recommendation:

In conclusion, all things considered, the sponsor has submitted a bare minimum of preclinical data. The results show that this orphan drug, which is related to coconut oil and a GRAS food supplement, very definitely dissolves cholesterol gallstones in vitro. However, following perfusion of the biliary tract in animals it has demonstrated some potential for direct local irritation and, when administered in a way that allowed direct access into the circulation (intralobular hepatic injection in rats), it elicited severe systemic effects (hemorrhagic pneumonitis and death). From the Pharmacology standpoint therefore, this NDA is approvable provided the labeling briefly mention the preclinical findings which suggest the possibility of local irritation with normal perfusion of the biliary tract and adverse systemic effects if administered in a way that permits direct access of the drug into the circulation.

Pierre Deslauriers

cc:
Orig:
HFN-102/VGlocklen
HFN-110
HFN-110/CSO
HFN-110/PDeslauriers/5/23/85
cb/5/23/85/0343v

CHEM

1, 9

Division of Cardio-Renal Drug Products
CHEMIST REVIEW NUMBER ONE

9

Completed: January 22, 1985

A. 1. NDA 19-368 ORIGINAL NEW DRUG APPLICATION

Applicant: Ascot Pharmaceuticals, Inc.
7701 N. Austin Avenue
Skokie, IL 60077
Telephone: (312) 967-1910
Arnold M. Schacter
V.P. - Technical/Regulatory Affairs

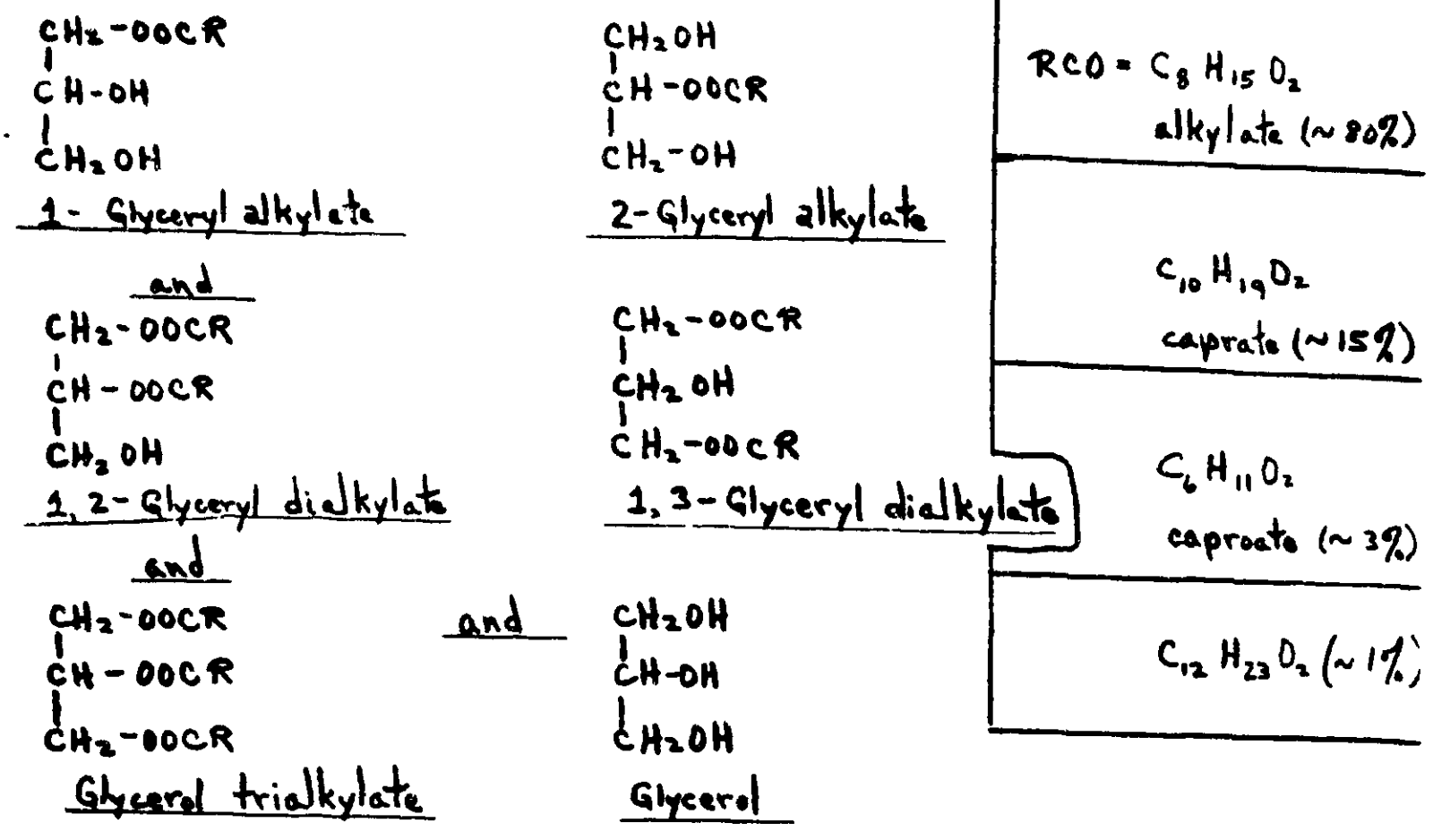
2. Product Names:

Proprietary: Moctan
Non-proprietary - None claimed, but such a name appears on labeling
Chemical: (a mixed mono-di glyceride)
glyceryl-1-mono-octanoate
glyceryl-1-mono-decanoate
glyceryl-1-2-di-octanoate
free glycerol

3. Dosage Form: A sterile, pyrogen-free liquid
Route of Administration: Perfusion into the common bile duct
Dispensed: Rx

4. Pharmacological Category - Solubilizing agent for cholesterol gallstones retained in the biliary tract following cholecystectomy.

5. Structural Formula



6. Classification: 1 B HV, Orphan Drug

B. 1. Initial Submission: September 14, 1984 date on FDA 356H
Received B/D: September 25, 1984
Assigned to Chemist: October 21, 1984

2. Amendments: None to date

3. Supporting:

4. Related: [redacted]

C. Remarks: When this review is accepted by the supervisory chemist the applicant will be promptly telephoned to discuss the deficiencies noted here. A letter to the applicant, reflecting the call, will be requested from the CSO, Mr. T.H. Hassall.

P.S. Telephone call was made January 25, 1985

D. Conclusions: Not approvable on chemistry and technical labeling. The firm will amend the NDA in response to the telephone call noted above.

Nathan R. Rosenthal, Ph.D.
Review Chemist HFN-110

cc
Orig.
HFN-102/CKumkumian
HFN-110
HFN-110/CSO
HFN-110/NRosenthal/1/22/85;3/1/85
sb/2/21/85;3/4/85/0518s
R/D: RWolters/1/23/85

Division of Cardio-Renal Drug Products
CHEMIST REVIEW NUMBER TWO

Completed: April 30, 1985

A. 1. NDA 19-368 ORIGINAL NEW DRUG APPLICATION - AS AMENDED

Applicant: Ascot Pharmaceuticals, Inc.
7701 N. Austin Avenue
Skokie, Illinois 60067

2. Product Name(s):

Proprietary: Moctan

Chemical: (a mixed mono-di glyceride)
glyceryl-1-mono-octanoate
glyceryl-1-mono-decanoate
glyceryl-1-2-di-octanoate
free glycerol

3. Drug Product: A sterile, pyrogen-free liquid.

Route of Administration: Perfusion into the common bile duct.

Dispensed: Rx

4. Pharmacological Category - Solubilizing agent for cholesterol gallstones retained in the biliary tract following cholecystectomy.

5. Structural Formula - Please refer to Chemist Review No. 1.

6. Classification: 1 B HV, Orphan Drug

B. 1. Initial Submission: September 14, 1984
Received B/D: September 25, 1984
Assigned to Chemist: October 21, 1984

2. Amendment: February 11, 1985 - in reply to telephone call January 25, 1985.

3. Supporting: [redacted]

4. Related: [redacted]

[redacted]

C. Remarks: [redacted]

D. Conclusions: The application, as amended, remains deficient on stability and technical labeling. Mr. Schacter was telephoned May 2, 1985 to tell him of the remaining dificiencies in detail. He will communicate with the FDA to correct the deficiencies that remain.

Nathan R. Rosenthal

Nathan R. Rosenthal, Ph.D.
Review Chemist, HFN-110

cc
Orig.
HFN-110
HFN-110/CSO
HFN-110/NRosenthal/4/30/85;5/3/85
sb/5/2/85;5/3/85/1001s
R/D: RWolters/5/2/85

[redacted]

30

Disivion of Cardio-Renal Drug Products
Chemist Review No. 3

Completed: May 14, 1984

A.1. NDA: 19-368 ORIGINAL NEW DRUG APPLICATION-AS AMENDED

Applicant: Ascot Pharmaceuticals, Inc.
7701 N. Austin Avenue
Skokie, Illinois 60067

2. Product Name(s)

Proprietary: MOCTAN
Chemical: (a mixed mono-diglyceride)
glyceryl-1- mono-octanoate
" -1 " -decanoate
" -1,2-di -octanoate
free glycerol

3. Drug Product: A sterile, pyrogen-free liquid
Route of Administration: Perfusion into the common bile duct.
Dispensed: Rx

4. Pharmacological Category: Solubilizing agent

5. Structural Formula: Please see Chemist Review No. 1

6. Classification: 1B HV, Orphan Drug.

B. 1. Initial Submission: September 14, 1984

2. Amendments: February 11, 1985: Please see Chemist Review No. 2
May 7, 1985: Please see this Chemist Review

C. Remarks: Mr. Arnold Schacter came to my office by appointment May 14, 1985. He submitted the amendment bearing the date May 7, 1985. This amendment is in reply to telephone conversations of May 2, 1985 and May 7 1985 pertaining to remaining deficiencies noted in Chemist review No. 2 of April 30, 1985.

D. Conclusion: The amendment dated May 7, 1985 provides all the information that has been found to be deficient in Chemist Review No. 2

Pending establishment inspection, this application now appears to be approvable from the standpoint of chemistry, manufacturing and controls, and technical labeling.

Methods validation has been initiated.
Establisment inspections have been requested

Nathan R. Rosenthal

Nathan R. Rosenthal, Ph.D.
Review Chemist, HFN-110

cc:
Orig:
HFN-110
HFN-110/CSO
HFN-110/NRosenthal/5/20/85
cb/5/20/85/0333v

5/30/85