



Study #25    Protocol: PK 4589    Report: GCR B-113'149

January 19, 1987

Possible Effects of Acitretin on Responses to IV Glucose Tolerance Test  
Conducted: May - September 1986  
Acitretin Capsule Formulation: 7080 lots G MZ 519 C01 and PT 9383 B01

InvestigatorAssay Lab

Objective To further study the interaction of acitretin on glycoregulation. An earlier study (study #24) has shown increased elimination of glucose from the blood in some subjects following IV administration of glucose together with a sulfonylurea agent. Improvement of glucose tolerance with a concurrent increase in sensitivity to insulin in psoriatic patients under etretinate therapy has been reported (Kang, et al., *Clin. Res.* 33:652 [Abstract]).

Study Design & Methods Six healthy male subjects, 22 - 25 years of age and within 10% of their ideal body weight, participated in this open study. The subjects did not remain overnight on the study site at any time. Alcohol intake was limited but not eliminated. Subjects were to fast unsupervised for 12 hours prior to initiation of infusions on Days 1, 10 and 25.

On Days 1, 10 and 25, each subject received a 10 minute IV infusion of 25 g of glucose. On Days 3 through 10, each subject orally received 50 mg of acitretin as two 25 mg capsules from formulation 7080, lots G MZ 519 C01 and PT 9383 B01. The acitretin doses were administered with 120 mL of water immediately prior to breakfast (not described) except for the dose on Day 10 which was not followed by breakfast. On Day 10 the acitretin administration was 30 minutes prior to the commencement of the IV administration.

On Days 1, 10 and 25, both insulin and blood glucose levels were measured predose and at 5, 10, 20, 30, 40, 50, 60, 70, 90, 120, 150 and 180 minutes post initiation of the IV administration. Additionally, on these Days, urine glucose levels were measured in a urine sample taken prior to starting the infusion and in an aliquot from urine collected over the first hour of the infusion. Trough levels of acitretin and its 13-cis metabolite were measured on Days 3, 5, 7, 9 and 10 with a plasma profiles on Day 10 consisting of samples from 0.5, 1, 2, 3, 4, 6, 8 and 10 hours post IV administration.

All manipulations with biological samples were carried out under light protection and plasma storage tubes for acitretin determinations were wrapped in aluminum foil. Plasma samples of acitretin and its 13-cis metabolite, 7652, were determined by the normal phase HPLC method described in Paravicini, et al., *J. Chromatogr. (Biomed. Appl)* 276:359 which has been described in earlier studies. Insulin determinations were performed radioimmunologically by use of a binding reagent. Blood glucose was measured by the glucose dehydrogenase method described Scholer, et al., *J. Clin. Chem. Clin. Biochem.* 14:189. The assay data is acceptable for a non-pivotal study of this nature.

Results The last IV infusion day which was designed for Day 25 occurred on days 22 through 25. No other protocol exceptions were noted.

No statistically significant differences were detected in time for blood glucose levels to return to baseline, the blood glucose elimination rate nor in the AUC above baseline for the blood glucose levels. Additionally, the AUC for serum insulin did not reveal statistically significant differences. Neither fasting urine glucose levels nor 1 hour urine collections revealed a statistically significant difference.

Since plasma levels of acitretin and its 13-cis metabolite were not collected under strictly supervised conditions, only gross observation may be made. While the firm feels that the trough level on Day 10 in subject (226 ng/mL) was erroneous, it appears to be confirmed by the 30 minute sample of 325 mg/mL. It seems likely that these subject was not compliant with the protocol.

### CONCLUSIONS

No effect of acitretin on IV glucose tolerance has been demonstrated in this limited study.

## DISSOLUTION

The firm has reported the following dissolution profile data which has been collected from 6 capsule units on USP Apparatus II (paddle) rotating at 50 rpm in 900 mL of 1% sodium lauryl sulfate in water at 37°C. The 25 mg capsules are represented by two formulations produced at Basle which differ only in the size of production, F-7 and F-8, and one formulation produced at Nutley, F-20. The 10 mg acitretin capsules are represented by two formulations produced in Basle which differ only in the size of production, F-9 and F-14.

	Average (CV) Range			
	5 min.	15 min.	30 min.	60 min.
<b>25 mg Capsules</b>				
Formulation F-7 (C-140715) [redacted] capsules produced)	57% (22%) 27 - 76%	82% (6%) 70 - 90%	88% (5%) 77 - 94%	91% (5%) 81 - 96%
Formulation F-8 (C-144946) [redacted] capsules produced)	42% (30%) 23 - 59%	88% (3%) 84 - 91%	91% (2%) 89 - 93%	95% (2%) 93 - 97%
Formulation F-20 (C-148657) (not reported)	15% (19%) 11 - 19%	41% (27%) 25 - 61%	64% (22%) 48 - 91%	89% (9%) 71 - 97%
<b>10 mg Capsules</b>				
Formulation F-9 (C-141675) [redacted] capsules produced)	49% (21%) 24 - 81%	101% (5%) 95 - 106%	107% (1%) 104 - 108%	107% (1%) 106 - 108%
Formulation F-14 (C-144956) [redacted] capsules produced)	34% (12%) 15 - 51%	92% (5%) 88 - 99%	98% (4%) 96 - 105%	102% (3%) 98 - 107%

Appendix D contains the firm's proposed dissolution method and specification and a detailed dissolution rate procedure. The only dissolution media that has been studied is 3% sodium lauryl sulfate in water. Bioequivalence has been demonstrated between 25 mg acitretin capsule formulation F-8 and F-20 in study S', protocol N3207B.

It should be noted that the 25 mg acitretin capsule formulation F-20 has not passed the firm's proposed dissolution specification. On page 1578 the 1990 USP XVII indicates that the acceptance criteria for stage S<sub>1</sub> where 6 capsules are tested is that each unit is not less than Q + 10%. Since the range of percent dissolution at 5 minutes for formulation F-20 is 71 - 97%, it is clear that at least one unit is less than the required Q + 10%, i.e. 81%.

In order to determine if an appropriate choice has been made for the dissolution specification, the firm should submit 3 additional dissolution profiles on the same lots and under the same conditions as above except that the media should be 1) water, 2) simulated gastric fluid without enzymes, and 3) simulated intestinal fluid without enzymes. However, the firm may submit solubility or other data that addresses the practicality of accomplishing these additional dissolution profiles.

LABELING

The following comments are based upon the firm's Revised DRAFT Package Insert which was submitted to the Agency on September 18, 1989.

### OVERALL CONCLUSIONS

1. The effect of food on acitretin absorption is prominent. Food enhances the extent of absorption by 90% and the rate of absorption by 70% while reducing the inter-subject variation in both of these parameters (protocol N2987B). Under fed conditions acitretin has been shown to be dose proportional after single doses of 25 mg, 50 mg, 75 mg and 100 mg (protocol N3147A). This proportionality does not hold when the single doses are administered under fasting conditions. Labeling should strongly reflect the need to be administered with food (protocol N2991A).

2. The 10 mg acitretin formulations which have been characterized pharmacokinetically and the 10 mg acitretin formulations which have been used in clinical safety and efficacy studies have been shown to be bioequivalent (protocol N3103A).
3. The bioequivalence linkage of the 25 mg acitretin formulations to be marketed and the 25 mg acitretin formulations which were studied in the clinical safety and efficacy studies requires evaluation of two studies: protocols N3103A and N3108B. Protocol N3103A has shown the 10 mg acitretin formulations used in clinical safety and efficacy studies to be bioequivalent to the acitretin formulations used in the biostudies that are to be marketed. Protocol N3108B has shown the 10 mg and 25 mg acitretin capsule formulation which are to be marketed to be proportionally equivalent in extent of absorption and similar in rate of absorption. The 90% confidence interval for the  $C_{max}$  of the 10 mg acitretin in comparison to the 25 mg acitretin capsule is (0.77, 0.96). While this is not bioequivalent in terms of rate of absorption, the Division of Biopharmaceutics does not feel that this difference is consequential.
4. An early 25 mg acitretin capsule formulation has been shown in study protocol PK-4514 to have an absolute bioavailability of 52% (N=5, range: 36-63%). The relative bioavailability of this 25 mg acitretin capsule formulation to a suspension was 86% with the suspension having absolute bioavailability of 72% (N=5, range: 47-92%). A more recent study (protocol N3108B) using the 10 mg and the 25 mg acitretin capsule formulations to be marketed has shown these formulations when normalized to be equivalent in extent of bioavailability to a 25 mg suspension. Using the 25 mg acitretin suspension as a standard for comparison, the absolute bioavailability of the acitretin capsule formulations to be marketed should be about 72%.
5. Interconversion of the 13-cis isomeric metabolite of acitretin to acitretin has been demonstrated by recovery of acitretin following administration of the 13-cis metabolite. This interconversion between the two compounds is thought to be responsible for the longer half-life determinations for acitretin following multiple dosing. The 13-cis metabolite has been shown to accumulate following multiple dosing while acitretin shows little accumulation. The longer half-life determinations for acitretin following multiple dosing appear to be reflective of a dynamic equilibrium between the two compounds (protocol PK 4472).
6. The average terminal half-life of acitretin has been determined to be 40 hours and that for its 13-cis metabolite is 64 hours. Due to the interconversion of the two compounds, the elimination of both compounds is necessary to provide for the elimination of acitretin from the body. The longest observed terminal half-life for either of the two compounds is 157 hours. Using this terminal half-life as the worst case, 99.8% of an administered dose will be eliminated at the end of 24 days with 0.195% remaining in the body. Additional confidence in these numbers comes from the mass balance study which demonstrated an average of 83% of the administered oral dose recovered in urine and feces at the end of 18 days (protocol PK 4535).
7. Differences exist in the bioavailability in an elderly group (n=8, 64-72 years) as compared to a young group (n=6, 24-32 years old). The single dose data indicates that acitretin is 49% more available to the elderly group than to the young group. The maximum concentration is 17% greater in the elderly group than in the young group (protocol PK-4515).
8. Neither acitretin nor its 13-cis metabolite were shown to have been removed during hemodialysis in 6 subjects with end-stage renal disease (protocol PK 4625).

## DEFICIENCIES

1. Labeling indicates that the maximum daily dose of acitretin may be as high as 75 mg while no multiple dose study to characterize this dosage regimen has been executed. A study of this nature is required for the 75 mg daily dosage regimen.
2. Since the effect on oral contraceptive has not been adequately studied and since it is foreseen that oral contraceptives will be used in order to avoid contraception while taking acitretin, the firm should commit to studying the possible effect of acitretin on oral contraceptives.
3. In order to determine if an appropriate choice has been made for the dissolution specification, the firm should submit 3 additional dissolution profiles on each of their product lots used in biostudies under the same conditions as given in the firm's dissolution procedure except that the media should be 1) water, 2) simulated gastric fluid without enzymes, and 3) simulated intestinal fluid without enzymes. The firm may submit solubility or other data that addresses the practicality of accomplishing these additional dissolution profiles.

The final dissolution specification cannot be set until those profiles have been submitted and reviewed. On an interim basis, not to exceed three months, the firm should follow the dissolution specification of Q = 80% at 45 minutes in 900 mL of 0.5% sodium lauryl sulfate in water at 37°C using USP Method II at 50 rpm.

## RECOMMENDATIONS

The Division of Biopharmaceutics has reviewed NDA 19-821 submissions dated Feb. 25, 1988, June 2, 1989, June 16, 1989, August 4, 1989 (2), August 30, 1989 and November 14, 1989 for acitretin 10 mg hard gelatin capsules and acitretin 25 mg hard gelatin capsules and has found that there are a number of acceptable biostudies that can be used to support the NDA for meeting the Agency's bioregulations (See Overall Conclusions above).

However, some additional pharmacokinetic studies are needed for the purpose of meeting the Agency's bio-regulations and for supporting the product's package insert labeling claims. (See deficiencies above.)

The Division of Biopharmaceutics is of the opinion that the required bio-studies should be conducted and reviewed prior to NDA approval. However, if HFD-520 feels the resolution of these issues is not critical for this NDA's approval then it is requested that the sponsor agree in writing to submit study protocols within 30 days of drug approval and agree in writing to initiate those studies within 90 days of receiving FDA's approval of those study protocols.

The firm should send samples (3 times 100 dosage units) of the commercial lot(s) evaluated in the sponsor's pivotal BA/BE studies for products being approved. Samples for additional proposed strengths not included in the BA/BE studies should also be submitted. The firm should provide the lot number(s), lot size(s), strength(s), date(s) of manufacture, and expiration date(s) for the samples submitted. For the lot(s) used in the BA/BE study(s), the study number(s) should be identified. These samples along with the above information should be sent to:

Biopharmaceutics Research Laboratory, HFD-424  
Federal Office Building 8, Room 2884  
200 C Street, SW  
Washington, D.C. 20204

These Recommendations, Overall Conclusions and Deficiencies should be forwarded to the firm.

*Jim McDowell 4-5-90*

Jim McDowell  
Pharmacokinetic Evaluation Branch

RD Initialed by See-Yan Lam, Pharm.D., Ph.D. 3-11-90  
FT Initialed by See-Yan Lam, Pharm.D., Ph.D. *See Yan 4-5-90*

cc: NDA 19-821 Orig., HFD-520(2), HFD-426(McDowell), HFD-344(Turner),  
HFD-19(FOI files), Drug, Chron and Reviewer files

JAM:jam:PC:N19-821D.50A:04-5-90