

Hormonal Contraceptive Interaction Studies and New Formulation PK

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Objective of Hormonal Contraception Interaction Studies

- To identify the isoenzymes responsible for the metabolism of isotretinoin and its metabolites.
- To assess the potential for isotretinoin or its metabolites to interact with hormonal contraception via a combination of *in vitro* and *in vivo* studies.

***In Vitro* Studies**

- Enzyme Identification
 - Recombinant P-450 isoenzymes
 - Pooled Liver Microsomes
- Specific Substrates
 - Medroxyprogesterone Acetate
 - No evidence of *in vitro* hepatocyte interaction
 - Progesterone
 - Report submitted-under review

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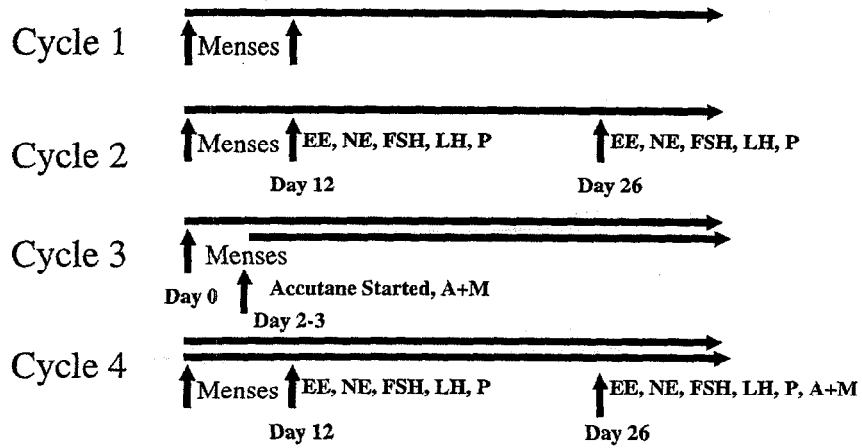
Features of *In Vivo* Studies

- Pharmacokinetic
 - Isotretinoin and Metabolites (steady-state)
 - Estrogen
 - Progestin
- Pharmacodynamic
 - FSH
 - LH
 - Progesterone

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Drug Interaction Study Design

Protocol NR15792 (Accutane NF) & Protocol NR15888 (Accutane)



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Interim Study Results

- Protocol NR15792 (Accutane NF)
 - PD Data from 9 subjects
 - Possible ovulation in 1 subject, awaiting more data
- Protocol NR15888 (Accutane)
 - PD and PK data from 22 subjects
 - No evidence of a PK or PD interaction

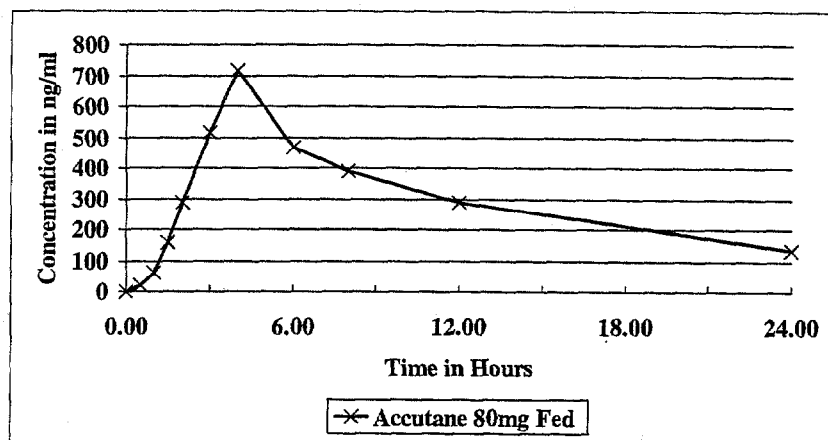
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Accutane vs. Accutane "NF" A Biopharmaceutic Perspective

- What is Accutane "NF"?
 - Accutane "NF" differs from Accutane® in that the active ingredient, isotretinoin, is present in the dosage form with a reduced particle size. This increases the overall solubility of isotretinoin by increasing its surface area.

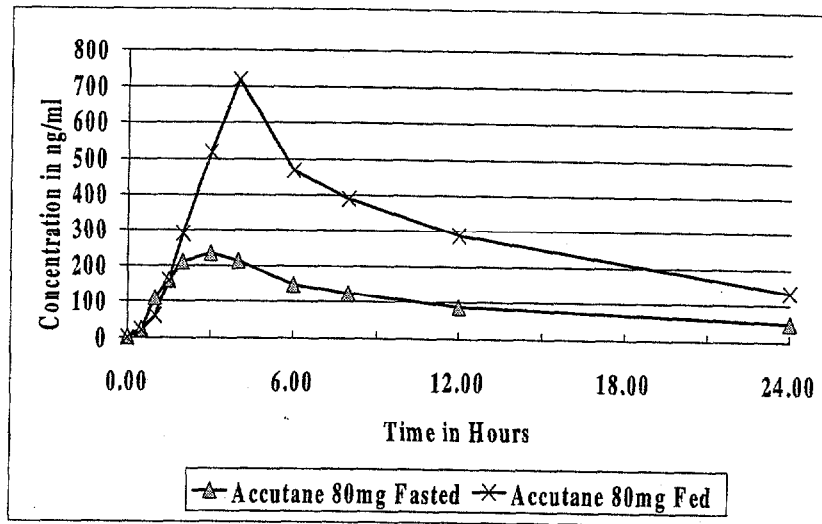
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Isotretinoin Plasma Levels



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Isotretinoin Plasma Levels



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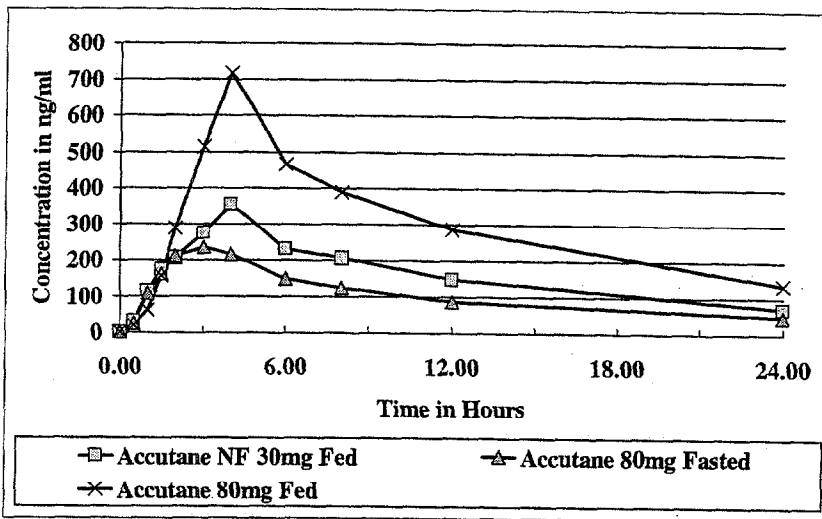
Accutane Food Effects

	Fed	Fasted	90% C.I.	Multiple*
	Accutane	Accutane		
Dose	80mg	80mg	n/a	n/a
AUC _{inf}	10004.43	3702.78	266-322	2.70
C _{max}	862.34	301.32	267-305	2.86
T _{max}	5.25	3.15	n/a	
C _v /F	8.4	25.38	n/a	0.34

*Test/Reference or Fed/Fasted

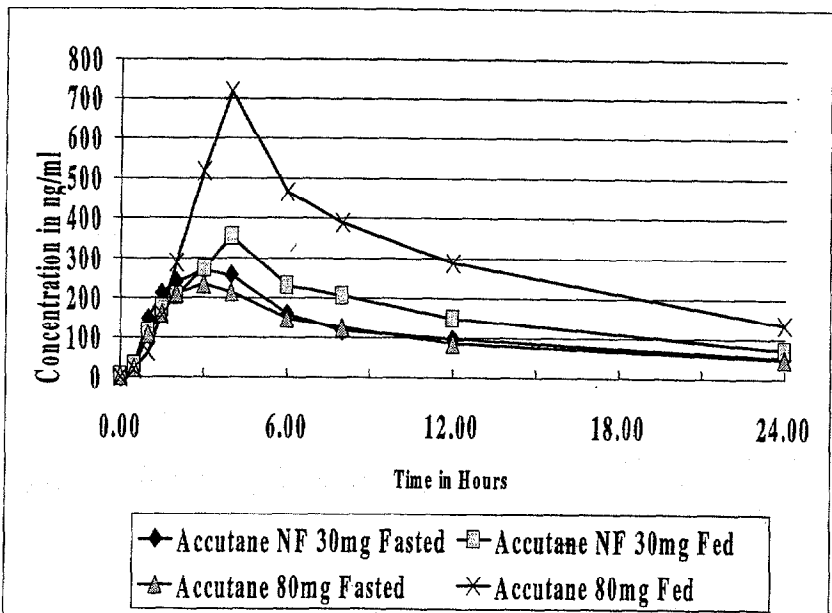
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Isotretinoin Plasma Levels



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Isotretinoin Plasma Levels



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Accutane "NF" vs. Accutane®

<i>Fasted</i>			
	<i>Accutane NF</i>	<i>Accutane</i>	<i>90% C.I.</i>
Dose	30mg	80mg	n/a
AUCinf	4182.69	3702.78	110-126
Cmax	336.17	301.32	105-128
Tmax	2.97	3.15	n/a
C _i /F	7.69	25.38	n/a

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Isotretinoin Relative Bioavailability

Based on AUC, on a mg per mg basis,
Accutane NF is approximately 33% more
bioavailable relative to currently marketed
Accutane, under clinical use conditions (i.e.
Accutane (FED) vs Accutane "NF" (Fasted)

1mg Accutane "NF" = 1.33mg Accutane (current)

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Accutane "NF" NDA

- NDA Contents
 - Dose Proportionality study of 7.5, 15, and 22.5mg dosage forms (as 15, 30 and 45mg doses)
 - Food Effect Studies
 - Formulation linkage studies
 - BE studies between proposed to-be-marketed and phase 3 drug product.

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Accutane NF Biopharmaceutics Summary

- Accutane NF as 7.5, 15, and 22.5mg caps are:
 - Dose Proportional (at 15, 30, and 45mg)
 - Has a significant food effect (~30% changes in AUC and Cmax), albeit less than that observed with Accutane
 - Equivalent between the proposed to-be-marketed and phase 3 studied drug product

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