CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-067

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-067	Submission Date(s): August 11, 2006
Brand Name	FLOPRED
Generic Name	Prednisolone Acetate Oral Suspension
Reviewer	Sally Y. Choe, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology II
OND division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Taro Pharmaceuticals U.S.A., Inc. b(4)
Relevant IND(s)	[redacted]
Submission Type; Code	505(b)2
Formulation; Strength(s)	5 mg / 5 mL and 15 mg / 5 mL Oral Suspension
Indication	Treatment of endocrine disorders; rheumatic disorders; [redacted] dermatologic diseases; allergic states; ophthalmic diseases; respiratory diseases; hematologic disorders; neoplastic diseases; [redacted] gastrointestinal diseases; b(4)

[redacted]

1. EXECUTIVE SUMMARY

1.1 RECOMMENDATION

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 22-067 for Prednisolone Acetate Oral Suspension and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the agency regarding the language in the package insert.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Prednisolone is a glucocorticoid, an adrenocortical steroid, which is typically well absorbed in gastrointestinal tract. Taro Pharmaceuticals U.S.A., Inc., the applicant, has formulated prednisolone acetate into Prednisolone [redacted] oral suspension that is in spill resistant syrup form. b(4)

The applicant submitted 505(b)2 NDA application for market approval of 5 mg/5 mL and 15 mg/5 mL strength Prednisolone [redacted] oral suspension. Approval is sought based on data from three bioequivalence studies comparing the prednsiolone NonSpil oral suspension with the currently marketed Prednisolone USP 5 mg tablet (ANDA 80-354) and Prednisolone USP 15 mg/5 mL syrup (ANDA 40-364) and 5 mg/5 mL syrup (ANDA 40-423). Watson Labs is the holder of ANDA 80-354 while KV Pharm is the holder of ANDAs 40-364 and 40-423. No separate Clinical Efficacy and Safety data was provided. . b(4)

The three bioequivalence studies are PEN-P5-319, PEN-P5-320, and PEN-P5-321. Studies PEN-P5-319 and -320 assessed bioequivalence of 15 mg doses of the NonSpil oral suspension (15 mg/5 mL) and the two reference products (syrup [15 mg/5 mL] and tablet [3x5 mg] products) under fasted condition and fed conditions, respectively. Study -321 assessed bioequivalence of 5 mg doses of the NonSpil oral suspension (5 mg/5 mL) and the two reference products (syrup [5 mg/5 mL] and tablet [1x5mg] products). The results of three studies demonstrate (as shown below) that 5 mg/5 mL and 15 mg/5 mL Prednisolone NonSpil suspensions are bioequivalent to same strength syrups and tablets under fasted condition. Also, the 15 mg/5 mL Prednisolone NonSpil suspension is bioequivalent to the same strength syrup and tablets under fed condition. Based on available information, it is reasonable to assume that 5 mg/5 mL strength prednisolone NonSpil oral suspension will also have similar food effect as that of the 15 mg//5 mL strength.

An Establishment Inspection was requested for the analytical site and the clinical site that conducted the bioequivalence study, PEN-P5-319. Inspection did not reveal any significant deficiencies at clinical and analytical sites that impact the study outcome.

1. Study PEN-P5-319: Single Dose Crossover Comparative Bioavailability Study of Prednisolone 15 mg/5 ml Suspension versus 15 mg/5 ml Syrup and versus 3 x 5 mg Tablets in Healthy Male and Female Volunteers / Fasting State

Prednisolone 15 mg (15 mg / 5 mL suspension versus 15 mg / 5 mL syrup and versus 3x5 mg tablets)

Geometric LS Means, Ratio and 90% Confidence Intervals							
Fasted Bioequivalence Study (PEN-P5-319)							
Parameter	Geometric LS Means			Ratio (%) Test vs Reference-1	90% C.I. (%) Test vs Reference-1	Ratio (%) Test vs Reference-2	90% C.I. (%) Test vs Reference-2
	Test* (15 mg / 5 mL suspension)	Reference-1* (15 mg / 5 mL syrup)	Reference-2* (3x5 mg tablets)				
C_{max}	298.20	345.00	308.72	86.44	82.76-90.27	96.59	92.49-100.88
AUC_T	1770.09	1700.64	1760.79	104.08	100.82-107.45	100.53	97.38-103-78
AUC_∞	1818.71	1745.80	1813.57	104.18	100.96-107.49	100.28	97.19-103.47

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞.

2. Study PEN-P5-320: Single Dose Crossover Comparative Bioavailability Study of Prednisolone 15 mg/5 ml Suspension versus 15 mg/5 ml Syrup and versus 3 x 5 mg Tablets in Healthy Male and Female Volunteers / Fed State

Prednisolone 15 mg (15 mg / 5 mL suspension versus 15 mg / 5 mL syrup and versus 3x5 mg tablets) Geometric LS Means, Ratio and 90% Confidence Intervals							
Fasted Bioequivalence Study (PEN-P5-320)							
Parameter	Geometric LS Means			Ratio (%) Test vs Reference-1	90% C.I. (%) Test vs Reference-1	Ratio (%) Test vs Reference-2	90% C.I. (%) Test vs Reference-2
	Test* (15 mg / 5 mL suspension)	Reference-1* (15 mg / 5 mL syrup)	Reference-2* (3x5 mg tablets)				
C_{max}	235.72	252.09	269.92	93.51	90.13-97.01	87.33	84.23-90.54
AUC_T	1956.86	1818.90	1756.10	107.58	103.45-111.89	111.43	107.22-115.81
AUC_∞	2023.74	1865.25	1804.51	108.50	104.27-112.90	112.15	107.85-116.62

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞.

3. Study PEN-P5-321: Single Dose Crossover Comparative Bioavailability Study of Prednisolone 5 mg/5 ml Suspension versus 5 mg/5 ml Syrup and versus 5 mg Tablets in Healthy Male and Female Volunteers / Fasting State

Prednisolone 5 mg (5 mg / 5 mL suspension versus 5 mg / 5 mL syrup and versus 5 mg tablet) Geometric LS Means, Ratio and 90% Confidence Intervals							
Fasted Bioequivalence Study (PEN-P5-321)							
Parameter	Geometric LS Means			Ratio (%) Test vs Reference-1	90% C.I. (%) Test vs Reference-1	Ratio (%) Test vs Reference-2	90% C.I. (%) Test vs Reference-2
	Test* (5 mg / 5 mL suspension)	Reference-1* (5 mg / 5 mL syrup)	Reference-2* (5 mg tablet)				
Cmax	157.85	175.70	172.23	89.84	86.25-93.58	91.65	87.99-95.47
AUCT	798.39	768.83	793.73	103.84	101.27-106.48	100.59	98.09-103.14
AUC∞	828.90	802.53	827.99	103.29	100.84-105.80	100.11	97.73-102.54

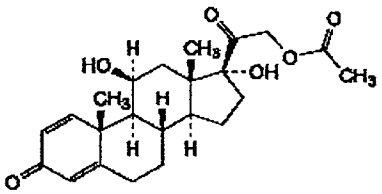
* units are ng mL for C_{max} and ng·h mL for AUC_T and AUC_∞.

2. QUESTION-BASED REVIEW (QBR)

2.1 GENERAL ATTRIBUTES

2.1.1. What are the chemical and physical-chemical properties of the drug substance?

Prednisolone acetate is one of the salt forms of prednisolone, a glucocorticoid, one of the adrenocortical steroids. Its chemical name is (11β)-11,17,21-Trihydroxypregna-1,4-diene-3,20-dione,21-Acetate. The molecular weight is 402.49 g/mol and its molecular formula is $C_{23}H_{30}O_6$. The following is its structural formula:



Prednisolone acetate appears as white to almost white, odorless powder. It is practically insoluble in water and in pH buffer solution ranging between [redacted] No polymorphic forms of prednisolone acetate are known [redacted] b(4)

2.1.1 What are the description and composition of the drug products?

Prednisolone Acetate Oral Suspensions 0.097% (equivalent to 5 mg/5 mL prednisolone base) and 0.293% (equivalent to 15 mg/5 mL prednisolone base) with cherry flavor are developed as NonSpil™ formulations for the US market by the applicant. This product does not require shaking to maintain product uniformity. List of all components of the dosage form, and their amounts on a per unit basis is as follows:

Strength (Label claim):	0.097% (w/w) equivalent to 5 mg/5 mL		0.293% (w/w) equivalent to 15 mg/5 mL	
Component and Quality Standard	Quantity per unit[1] (mg/5 ml)	%	Quantity per unit[1] (mg/5 ml)	%
Purified water, USP[2]				
EDTA Disodium, USP				
Carbomer 934P [redacted] [3]				
Sorbitol crystalline, NF				
Glycerin, USP				
Sucralose liquid concentrate[4]				
Masking agent [redacted]				
Cherry flavor [redacted]				
Butylparaben, NF				
Sodium hydroxide, NF				
Poloxamer 188, NF				
Propylene glycol, USP				
Prednisolone Acetate, USP [5]				
Total Weight / Volume	--	100	--	100

b(4)

[1] Quantity per unit calculated after [redacted]

[2] Amount of purified water [redacted]

[3] Amount of Carbomer [redacted]

[4] Sucralose [redacted]

[5] Masking Agent [redacted] b(4)

[6] Cherry Flavor is a [redacted]

[7] Amount of NaOH is based on [redacted]

[8] 5.56 mg and 16.82 mg are equivalent to 5 mg and 15 mg prednisolone, respectively.

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Prednisolone is a synthetic adrenocortical steroid drug with predominantly glucocorticoid properties. The pharmacological effects of prednisolone include: promotion of gluconeogenesis; increased deposition of glycogen in the liver; inhibition of the utilization of glucose; anti-insulin activity; increased catabolism of protein; increased lipolysis; stimulation of fat synthesis and storage; increased glomerular filtration rate and resulting increase in urinary excretion of urate; and increased calcium excretion. In addition, inflammatory processes and the later stages of wound healing are inhibited. The therapeutic indications for prednisolone are treatment of endocrine disorders, rheumatic disorders, [redacted] dermatologic diseases, allergic states, ophthalmic diseases, respiratory diseases, hematologic disorders, neoplastic diseases, [redacted] b(4) [redacted] gastrointestinal diseases, [redacted]

2.1.3. What is the proposed route of administration?

Prednisolone acetate oral suspension is formulated to be taken orally.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What is the pharmacokinetics of prednisolone?

The following information comes from Prednisolone sodium phosphate, USP, oral solution label and various literature references.

Absorption:

Prednisolone is rapidly and well absorbed from the gastrointestinal tract following oral administration.

Distribution:

Prednisolone is 70-90% protein-bound in the plasma.

Metabolism:

Prednisolone is metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates.

Elimination:
The elimination half-life of prednisolone is normally 2 to 4 hours.

2.2.2 Was a waiver for a pediatric trial granted?

The Division of Anesthesia, Analgesia and Rheumatology Products has requested the justification for the sponsor's request for a waiver for pediatric studies.

2.3 INTRINSIC FACTORS

Prednisolone acetate oral suspension is designed to be bioequivalent to other oral products such as Prednisolone syrup and tablets and the influence of any intrinsic factors would be expected to be the same as indicated for Prednisolone syrup and tablets and are reflected in the label.

2.4 EXTRINSIC FACTORS

The influence of extrinsic factors and/or impact of any difference in exposure would be expected to be the same as for Prednisolone syrup and tablets. These issues are covered in the labeling in the same way as for Prednisolone syrup and tablets.

2.5 ANALYTICAL SECTION

2.5.1 What bioanalytical methods are used to assess concentrations?

A validated HPLC/MS method was employed for the analysis of prednisolone in human plasma. Prednisolone free base and the internal standard, [redacted] were extracted by liquid-liquid extraction. The lower limit of quantitation for morphine was 5 ng/mL. The bioanalytical determinations were performed at [redacted] b(4)
The analytical method used has been shown to be sensitive, accurate and selective for the plasma level determination of prednisolone in the concentration range of [redacted] There are no concerns with the assay methodology.

2.5.2 What information is available to assure that both the analytical assay and the clinical study were performed according to current GMPs and GCPs?

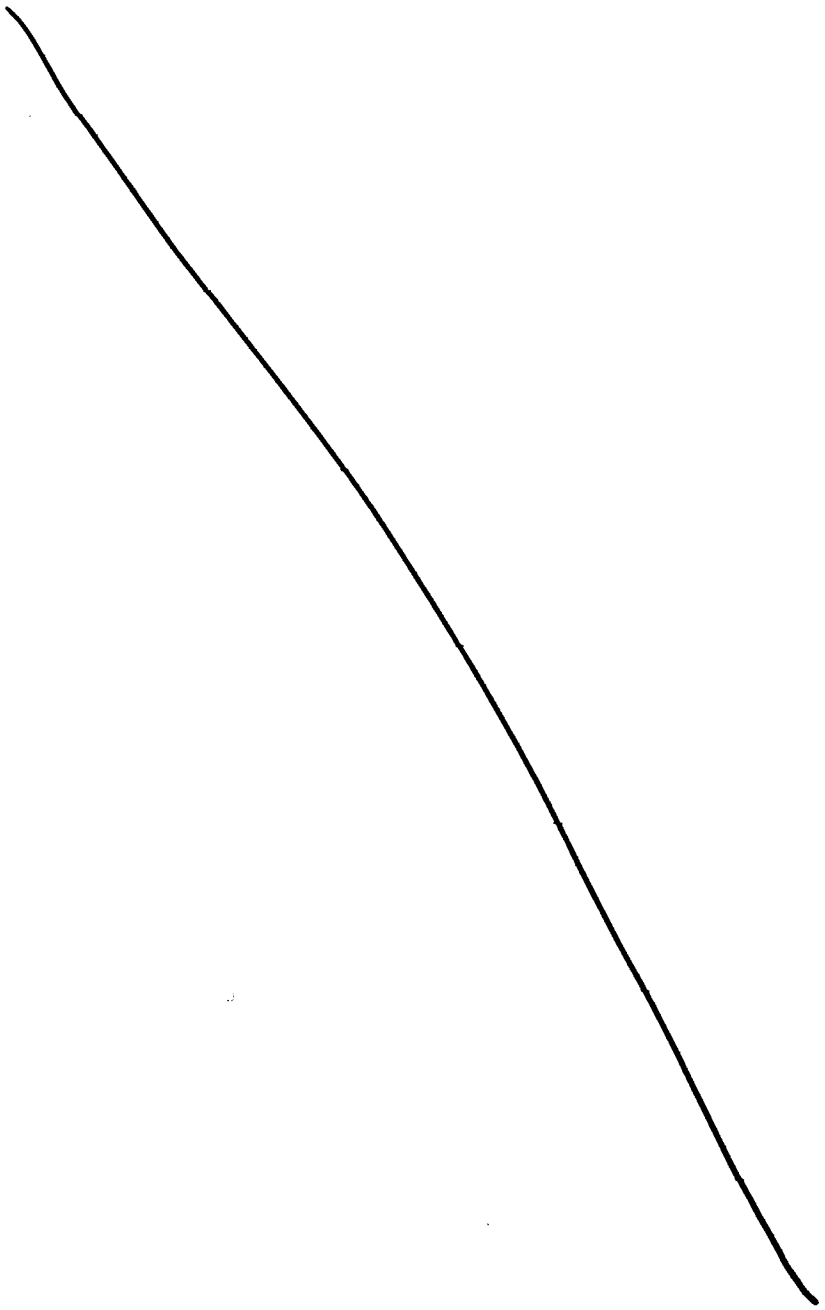
An Establishment Inspection was requested for the analytical site and the clinical site.

2.5.3 Did the Office of Compliance (Division of Scientific Investigations-Bioequivalence) report reveal any deficiencies that may affect the outcome of the bioequivalence study submitted by the firm?

No. Inspection did not reveal any significant deficiencies at clinical and analytical sites that impact the study outcome. Please see the memorandum by Dr. Nilufer Tampal dated April 26, 2007 for details.

3. DETAILED LABELING RECOMMENDATIONS

FLOPRED has shown to be bioequivalent to other oral products such as Prednisolone syrup and tablets. The detailed labeling recommendation in yellow highlight in Clinical Pharmacology section reflects these study results. The labeling is being updated jointly by the Study Endpoint and Label Development (SEALD) team and the review team.



b(4)

b(4)

18 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

4.2 INDIVIDUAL STUDY REVIEWS

4.2.1 Bioequivalence Study: Fasted 15 mg / 5 mL suspension

Clinical Study PEN-P5-319

TITLE: Single Dose Crossover Comparative Bioavailability Study of Prednisolone 15 mg/5 mL Suspension versus 15 mg / 5 mL Syrup and versus 3 x 5 mg Tablets in Healthy Male and Female Volunteers / Fasting state

INVESTIGATOR: b(4)

STUDY CENTER:

PHARMACOKINETIC AND STATISTICAL ANALYSIS: b(4)

BIOANALYTICAL ANALYSIS: b(4)

STUDY PERIOD: January 5 to January 21, 2006

OBJECTIVE: The objective of the study was to evaluate and compare the relative bioavailability and therefore the bioequivalence of three formulations of prednisolone after a single oral dose administration under fasting conditions.

STUDY DESIGN: This is a single center, randomized, single dose, laboratory-blinded, 3-period, 6-sequence, crossover study in healthy male and female subjects. In each study period, following an overnight fast of at least 10 hours, the assigned treatment was orally administered with 240 mL of water. Subjects continued fasting for 4 hours after each dose. Water was not permitted from 2 hour before dosing and until 2 hour after dosing. The washout period was at least 7 days and this was sufficient based on prednisolone's elimination half-life of 2 to 4 hours.

Drug Code:	A= Test	B= Reference-1	C= Reference-2
Formulation:	Prednisolone Acetate NonSpil™ 15 mg/5 mL suspension	PrednisoLONE USP 15 mg/5 mL syrup	Prednisolone USP 5 mg tablet
Manufacturer:	Taro Pharmaceuticals Inc., Canada	[redacted]	
Batch No.:	S209-56311	62046	C4J0909
Manufacturing Date:	N/AV	N/AV	N/AV
Expiry Date:	N/AV	11/2006	OCT 2006
Measured Content:	[redacted]		

b(4)

BLOOD SAMPLE COLLECTION: 7 mL of blood were collected in pre-cooled K_3 EDTA Vacutainers at pre-dose, and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

SAFETY ASSESSMENT: Safety parameters included the occurrence of adverse events and clinical laboratory parameters. Tests for hematology, blood chemistry and urinalysis were carried out in accordance with standard operating procedures of the licensed laboratory of [redacted] For female volunteers, pregnancy tests were also performed prior to, during the study and at post-study.

b(4)

SUBJECTS: Twenty-four normal healthy, male and female subjects (11 males and 13 females) were randomized and completed the study. Subjects were between the ages of 20 and 72 years (mean + SD = 37 + 14 years).

ANALYTICAL METHOD: A validated HPLC/MS method was employed for the analysis of prednisolone in human plasma. Prednisolone free base and the internal standard, [redacted] were extracted by liquid-liquid extraction. A set of eight point calibration curve covering the range of [redacted], and quality control samples at concentrations of 15.00, 100.00, and 375.00 ng/mL were prepared with drug free human plasma. Average back-calculated standards had %CV of [redacted] The range of correlation coefficient for analytical runs was [redacted] and the inter-assay %CV for QC ranged from [redacted] There were 68 repeat samples out of 1440 samples due to inadequate chromatography, sample being lost in processing, greater than upper limit of quantitation, or unacceptable internal standard response. These repeats did not have significant impact on conclusion of the study.

b(4)

PHARMACOKINETICS

Statistical Methods: A sample size of 24 was recommended to meet the 80 – 125% confidence interval limits with a statistical power of at least 80% if the expected Cmax and AUC_T ratio were to fall between 92.5 and 107.5%. The pharmacokinetic parameters reported were C_{max}, AUC_{0-t}, AUC_T, $AUC_{T,\infty}$, K_{el}, T_{max}, and $T_{1/2el}$.

Statistical and PK analyses were performed using Kinetic, version 3.00.013, an application developed at [redacted] and SAS version [redacted]

b(4)

All PK parameters were analyzed by the analysis of variance (ANOVA) in which treatment, sequence, period and period-by-treatment interaction as well as the left-over interaction terms between the three factors were modeled as fixed effects. The relative geometric mean and the 90% confidence interval of the relative geometric mean of C_{max}, AUC_{∞}, and AUC_T of the Test to each Reference products were calculated for the assessment of bioequivalence.

Results:

The summary of the pharmacokinetic parameters for prednisolone and the results of bioequivalence testing are given in the following tables.

Table 8. Summary of Main Study Results Prednisolone 15 mg/5 mL Suspension vs Syrup

PARAMETER	TEST		REFERENCE		t (treatment)	p
	MEAN	C.V.	MEAN	C.V.		
C_{max} (ng/mL)	321.08	52.0	362.35	37.8	-4.24	<0.001
ln (C_{max}) (ng/mL)	5.6978	6.0	5.8435	5.1	-5.65	<0.001
T_{max} (hours)	2.00	31.2	0.75	35.3	10.31	<0.001
AUC_T (ng·h/mL)	1945.53	59.8	1822.71	49.8	2.23	<0.05
ln (AUC_T) (ng·h/mL)	7.4788	5.1	7.4388	4.5	2.12	<0.05
AUC_{∞} (ng·h/mL)	1999.40	60.0	1872.68	50.4	2.24	<0.05
ln (AUC_{∞}) (ng·h/mL)	7.5059	5.1	7.4650	4.5	2.20	<0.05
$AUC_{T/\infty}$ (%)	97.33	1.1	97.42	1.1	-0.38	N.S.
K_{el} ($hour^{-1}$)	0.2598	18.4	0.2578	18.9	0.50	N.S.
$T_{1/2el}$ (hours)	2.78	23.3	2.81	24.9	-0.70	N.S.

For T_{max}, the median is presented and the statistical analysis is based on ranks.
N.S.= Not Significant ($p > 0.05$)

Table 9. Comparison of Results with Standards for Bioequivalence Prednisolone 15 mg/5 mL Suspension vs Syrup

PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	298.20	345.00	86.44	82.76	90.27
AUC_T	1770.09	1700.64	104.08	100.82	107.45
AUC_∞	1818.71	1745.80	104.18	100.96	107.49

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Table 10. Summary of Main Study Results Prednisolone 15 mg/5 mL Suspension vs 3 x 5 mg Tablets

PARAMETER	TEST		REFERENCE		t (treatment)	p
	MEAN	C.V.	MEAN	C.V.		
C_{max} (ng/mL)	321.08	52.0	326.91	43.5	-0.60	N.S.
ln (C_{max}) (ng/mL)	5.6978	6.0	5.7324	5.4	-1.34	N.S.
T_{max} (hours)	2.00	31.2	1.00	65.5	3.14	<0.01
AUC_T (ng·h/mL)	1945.53	59.8	1910.13	54.3	0.64	N.S.
ln (AUC_T) (ng·h/mL)	7.4788	5.1	7.4735	4.8	0.28	N.S.
AUC_∞ (ng·h/mL)	1999.40	60.0	1968.43	54.6	0.55	N.S.
ln (AUC_∞) (ng·h/mL)	7.5059	5.1	7.5031	4.8	0.15	N.S.
$AUC_{T/\infty}$ (%)	97.33	1.1	97.10	1.3	1.03	N.S.
K_{el} ($hour^{-1}$)	0.2598	18.4	0.2583	19.3	0.38	N.S.
$T_{1/2el}$ (hours)	2.78	23.3	2.81	25.5	-0.73	N.S.

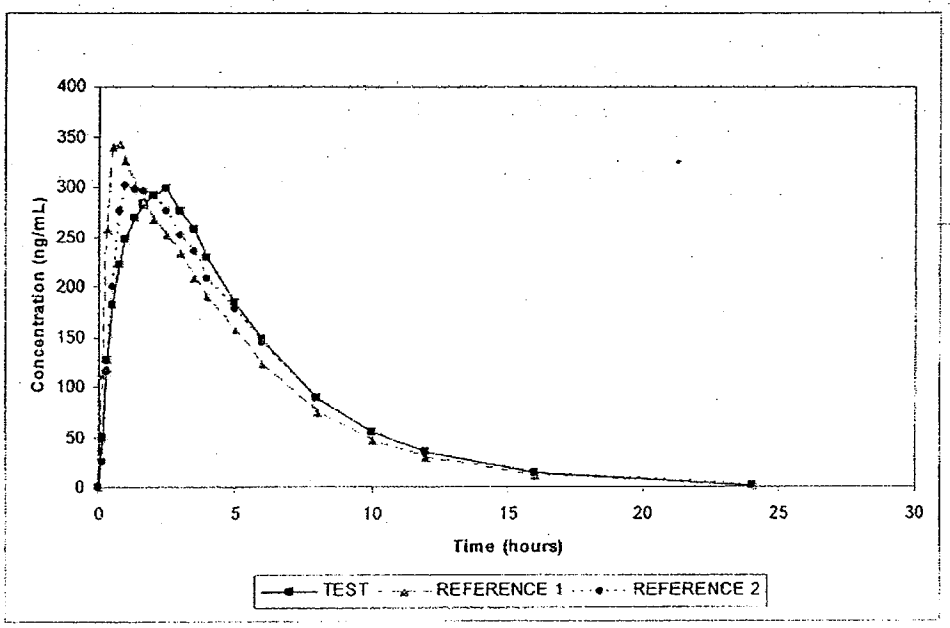
For T_{max}, the median is presented and the statistical analysis is based on ranks.
N.S. = Not Significant ($p > 0.05$)

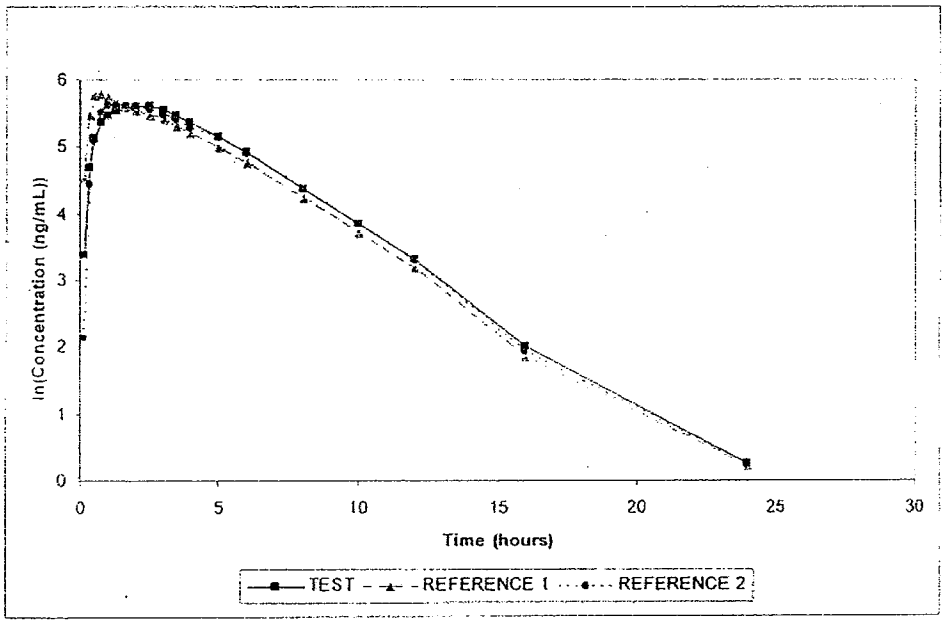
Table 11. Comparison of Results with Standards for Bioequivalence Prednisolone 15 mg/5 mL Suspension vs 3 x 5 mg Tablets

PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	298.20	308.72	96.59	92.49	100.88
AUC_T	1770.09	1760.79	100.53	97.38	103.78
AUC_∞	1818.71	1813.57	100.28	97.19	103.47

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Best Possible Copy





SAFETY ASSESSMENT: Eleven out of 24 subjects participating in the trial reported adverse events including abnormal laboratory values throughout the study. The intensity of the events ranged from mild to moderate. Similar number of subjects reported the AEs after each treatment (9 for Test, 6 for Reference B, and 7 for Reference C). Overall, the tolerability of the study drug products was acceptable.

CONCLUSION:

- The test product of Prednisolone Acetate Nonspil 15 mg/5 mL suspension is bioequivalent to the reference products, PrednisoLONE USP 15 mg/5 mL syrup [redacted]) and Prednisolone USP 5 mg tablets [redacted] under fasted condition. b(4)
- There were no significant safety issues in each treatment of Prednisolone suspension, syrup, and tablets.

4.2.2 Bioequivalence Study: Fed 15 mg / 5 mL suspension

Clinical Study PEN-P5-320

TITLE: Single Dose Crossover Comparative Bioavailability Study Of Prednisolone 15 mg / 5 mL Suspension versus 15 mg / 5 mL Syrup and versus 3 x 5 mg Tablets In Healthy Male and Female Volunteers / Fed State

INVESTIGATOR:

STUDY CENTER: [redacted] b(4)

PHARMACOKINETIC AND STATISTICAL ANALYSIS:

[redacted] b(4)

BIOANALYTICAL ANALYSIS:

[redacted] b(4)

STUDY PERIOD: February 27 to March 15, 2006

OBJECTIVE: The objective of the study was to evaluate and compare the relative bioavailability and therefore the bioequivalence of three formulations of prednisolone after a single oral dose administration under fed conditions.

STUDY DESIGN: This is a single center, randomized, single dose, laboratory-blinded, 3-period, 6-sequence, crossover study in healthy male and female subjects. In each study period, following an overnight fast, subjects received a standardized high-fat, high-calorie meal 30 minutes before the assigned treatment. The subjects were to eat the total content of this meal in 30 minutes or less. The meal was comprised of 240 mL of whole milk, 2 eggs fried in butter, 4 ounces of has brown potatoes (2 potato patties), 2 slices of toast with 14 g of butter, and 2 strips of bacon. The washout period between the treatments was at least 7 days and this was sufficient based on prednisolone's elimination half-life of 2 to 4 hours.

Drug Code:	A= Test	B= Reference-1	C= Reference-2
Formulation:	Prednisolone Acetate NonSpil™ 15 mg/5 mL suspension	PrednisoLONE USP 15 mg/5 mL syrup	Prednisolone USP 5 mg tablet
Manufacturer:	[redacted]		
Batch N°:	S209-56311	62046	C4J0909
Manufacturing Date:	N/AV	N/AV	N/AV
Expiry Date:	N/AV	11/2006	OCT 2006
Measured Content of label claim:	[redacted]		

b(4)

BLOOD SAMPLE COLLECTION: 7 mL of blood were collected in pre-cooled K_3 EDTA Vacutainers at pre-dose, and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.33, 3.67, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

SAFETY ASSESSMENT: Safety parameters included the occurrence of adverse events and clinical laboratory parameters. Tests for hematology, blood chemistry and urinalysis were carried out in accordance with standard operating procedures of the licensed laboratory of [redacted] For female volunteers, pregnancy tests were also performed prior to, during the study and at post-study.

b(4)

SUBJECTS: Twenty-four normal healthy, male and female subjects (12 males and 12 females) were randomized and completed the study. Subjects were between the ages of 22 and 63 years (mean ± SD = 43 ± 13 years).

ANALYTICAL METHOD: A validated HPLC/MS method was employed for the analysis of prednisolone in human plasma. Prednisolone free base and the internal standard, [redacted] were extracted by liquid-liquid extraction. A set of eight point calibration curve covering the range of [redacted] and quality control samples at concentrations of 15.00, 100.00, and 375.00 ng/mL were prepared with drug free human plasma. Average back-calculated standards had %CV of [redacted] The range of correlation coefficient for analytical runs was [redacted], and the inter-assay %CV for QC ranged from [redacted]. There were 2 repeat samples out of 1420 analyzed samples due to sample being lost in processing. These repeats did not have significant impact on conclusion of the study.

b(4)

PHARMACOKINETICS

Statistical Methods: A sample size of 24 was recommended to meet the 80 – 125% confidence interval limits with a statistical power of at least 80% if the expected Cmax and AUC_T ratio were to fall between 92.5 and 107.5%. The pharmacokinetic parameters reported were C_{max}, $AUC_{...}$, AUC_T, $AUC_{T-...}$, K_{el}, T_{max}, and $T_{1/2el}$.

Statistical and PK analyses were performed using Kinetic, version 8.00.007, an application developed at [redacted] and SAS version [redacted]

b(4)

All PK parameters were analyzed by the analysis of variance (ANOVA) in which treatment, sequence, period and period-by-treatment interaction as well as the left-over interaction terms between the three factors were modeled as fixed effects. The relative geometric mean and the 90% confidence interval of the relative geometric mean of C_{max}, AUC_{∞}, and AUC_T of the Test to each Reference products were calculated for the assessment of bioequivalence.

Results:

Twenty-three subjects received all three treatments. One subject completed tablets and suspension treatments only because she withdrew her consent for personal reasons before dosing of period 3. The summary of the pharmacokinetic parameters for prednisolone and the results of bioequivalence testing are given in the following tables.

Table 8. Summary of Main Study Results Prednisolone 15 mg/5 mL Suspension vs Syrup

PARAMETER	TEST		REFERENCE-1		t (treatment)	p
	MEAN	C.V.	MEAN	C.V.		
C_{max} (ng/mL)	240.73	21.8	253.14	22.1	-3.19	<0.01
ln (C_{max}) (ng/mL)	5.4626	3.8	5.5125	3.8	-3.08	<0.01
T_{max} (hours)	3.33	33.7	2.50	27.1	1.22	N.S.
AUC_T (ng·h/mL)	2086.20	40.5	1843.76	31.8	2.64	<0.05
ln (AUC_T) (ng·h/mL)	7.5791	4.6	7.4761	3.9	3.14	<0.01
AUC_∞ (ng·h/mL)	2158.32	40.4	1889.73	31.4	2.93	<0.01
ln (AUC_∞) (ng·h/mL)	7.6127	4.6	7.5014	3.9	3.46	<0.01
$AUC_{T/\infty}$ (%)	96.71	1.7	97.52	1.7	-1.85	N.S.
K_{el} ($hour^{-1}$)	0.2412	20.1	0.2524	21.4	-1.31	N.S.
$T_{1/2el}$ (hours)	3.00	23.1	2.91	29.7	0.51	N.S.

For T_{max}, the median is presented and the statistical analysis is based on ranks.
N.S.= Not Significant (p> 0.05)

Table 9. Comparison of Results with Standards for Bioequivalence Prednisolone 15 mg/5 mL Suspension vs Syrup

PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE-1		LOWER	UPPER
C_{max}	235.72	252.09	93.51	90.13	97.01
AUC_T	1956.86	1818.90	107.58	103.45	111.89
AUC_∞	2023.74	1865.25	108.50	104.27	112.90

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Best Possible Copy

Table 10. Summary of Main Study Results Prednisolone 15 mg/5 mL Suspension vs 3 x 5 mg Tablets

PARAMETER	TEST		REFERENCE-2		t (treatment)	p
	MEAN	C.V.	MEAN	C.V.		
C_{max} (ng/mL)	240.73	21.8	275.43	21.4	-6.31	<0.001
ln (C_{max}) (ng/mL)	5.4626	3.8	5.5981	3.6	-6.32	<0.001
T_{max} (hours)	3.33	33.7	2.00	57.3	4.23	<0.001
AUC_T (ng·h/mL)	2086.20	40.5	1826.84	30.8	4.14	<0.001
ln (AUC_T) (ng·h/mL)	7.5791	4.6	7.4709	3.7	4.73	<0.001
AUC_∞ (ng·h/mL)	2158.32	40.4	1878.70	31.2	4.32	<0.001
ln (AUC_∞) (ng·h/mL)	7.6127	4.6	7.4980	3.8	4.95	<0.001
$AUC_{T/\infty}$ (%)	96.71	1.7	97.33	1.3	-1.48	N.S.
K_{el} ($hour^{-1}$)	0.2412	20.1	0.2603	15.2	-2.84	<0.01
$T_{1/2el}$ (hours)	3.00	23.1	2.73	17.8	2.33	<0.05

For T_{max}, the median is presented and the statistical analysis is based on ranks.
N.S.= Not Significant (p> 0.05)

Table 11. Comparison of Results with Standards for Bioequivalence Prednisolone 15 mg/5 mL Suspension vs 3 x 5 mg Tablets

PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE-2		LOWER	UPPER
C_{max}	235.72	269.92	87.33	84.23	90.54
AUC_T	1956.86	1756.10	111.43	107.22	115.81
AUC_∞	2023.74	1804.51	112.15	107.85	116.62

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Figure 1. Linear Profile of the Mean

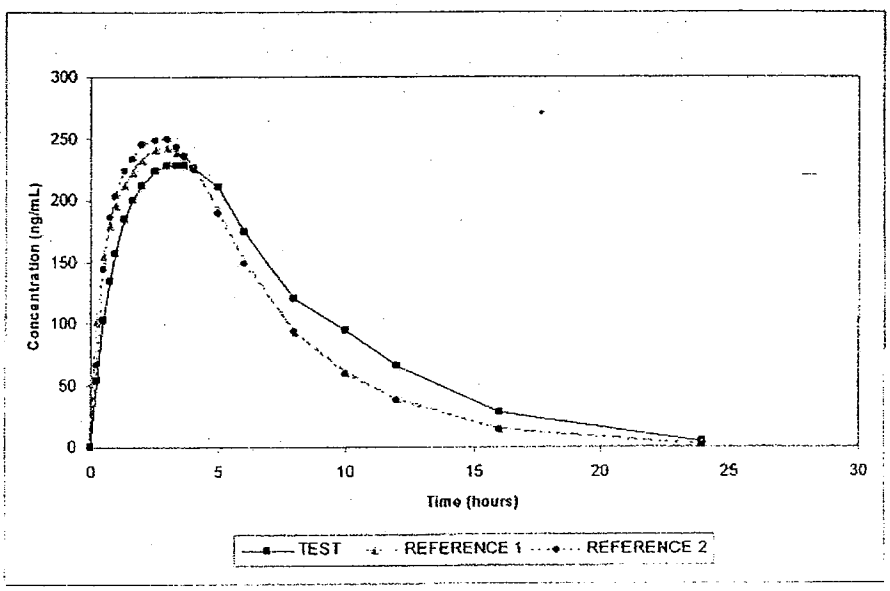
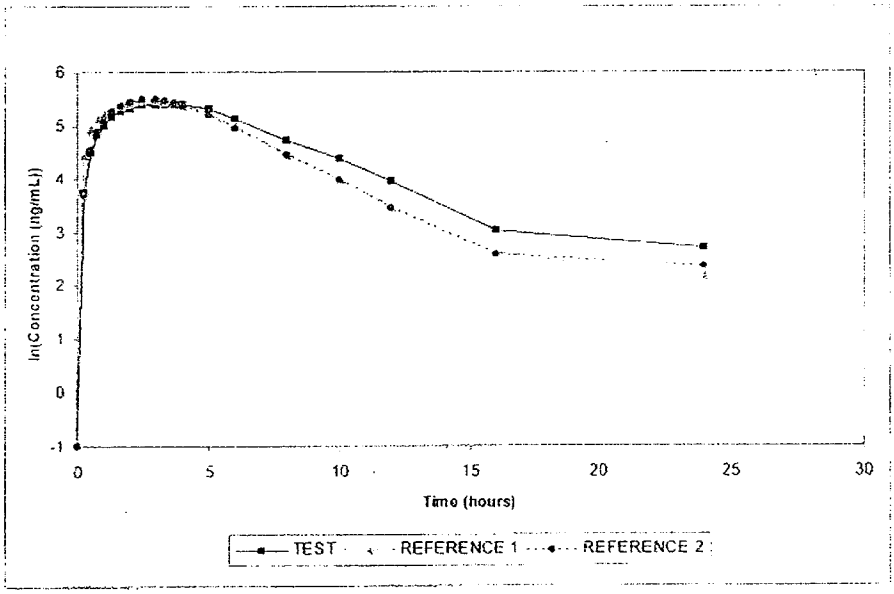


Figure 2. Logarithmic Profile of the Mean



SAFETY ASSESSMENT: Thirteen out of 24 subjects participating in the trial reported adverse events throughout the study. The intensity of the events ranged from mild to moderate. Similar number of subjects reported the AEs after each treatment (9 for Test, 6 for Reference B, and 10 for Reference C). Overall, the tolerability of the study drug products was acceptable.

CONCLUSION:

- The test product of Prednisolone Acetate Nonspil 15 mg/5 mL suspension is bioequivalent to the reference products, PrednisoLONE USP 15 mg/5 mL syrup [redacted] and Prednisolone USP 5 mg tablets [redacted] under fed condition. b(4)
- There were no significant safety issues in each treatment of Prednisolone suspension, syrup, and tablets.

4.2.3 Bioequivalence Study: Fasted 5 mg / 5 mL suspension

Clinical Study PEN-P5-321

TITLE: Single Dose Crossover Comparative Bioavailability Study of Prednisolone 5 mg / 5 mL Suspension versus 5 mg / 5 mL Syrup and versus 5 mg Tablets in Healthy Male and Female Volunteers Following a 5 mg Administration / Fasting State

INVESTIGATOR:

STUDY CENTER: [redacted] b(4)

PHARMACOKINETIC AND STATISTICAL ANALYSIS:

[redacted] b(4)

BIOANALYTICAL ANALYSIS:

[redacted] b(4)

STUDY PERIOD: April 28 to May 14, 2006

OBJECTIVE: The objective of the study was to evaluate and compare the relative bioavailability and therefore the bioequivalence of three formulations of prednisolone after a single oral dose administration under fasting conditions.

STUDY DESIGN: This is a single center, randomized, single dose, laboratory-blinded, 3-period, 6-sequence, crossover study in healthy male and female subjects. In each study period, following an overnight fast of at least 10 hours, the assigned treatment was orally administered with 240 mL of water. Subjects continued fasting for 4 hours after each dose. Water was not permitted from 2 hour before dosing and until 2 hour after dosing. The washout period was at least 7 days and this was sufficient based on prednisolone's elimination half-life of 2 to 4 hours.

Drug Code:	A= Test	B= Reference-1	C= Reference-2
Formulation:	Prednisolone Acetate NonSpil™ 5 mg/5 mL suspension	PrednisoLONE USP 5 mg/5 mL syrup	Prednisolone USP 5 mg tablet
Manufacturer:		[redacted]	
Batch No.:	S194-56309	61078	C4J0909
Manufacturing Date:	N/AV	N/AV	N/AV
Expiry Date:	N/AV	12/2006	Oct 2006
Measured Content:		[redacted]	

b(4)

BLOOD SAMPLE COLLECTION: 7 mL of blood were collected in pre-cooled K_3 EDTA Vacutainers at pre-dose, and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose.

SAFETY ASSESSMENT: Safety parameters included the occurrence of adverse events and clinical laboratory parameters. Tests for hematology, blood chemistry and urinalysis were carried out in accordance with standard operating procedures of the licensed laboratory of [redacted] For female volunteers, pregnancy tests were also performed prior to, during the study and at post-study.

b(4)

SUBJECTS: Twenty-four normal healthy, male and female subjects (11 males and 13 females) were randomized and completed the study. Subjects were between the ages of 27 and 71 years (mean + SD = 49 + 14 years).

ANALYTICAL METHOD: A validated HPLC/MS method was employed for the analysis of prednisolone in human plasma. Prednisolone free base and the internal standard. [redacted] were extracted by liquid-liquid extraction. A set of eight point calibration curve covering the range of [redacted] and quality control samples at concentrations of 15.00, 100.00, and 375.00 ng/mL were prepared with drug free human plasma. Average back-calculated standards had %CV of [redacted] The range of correlation coefficient for analytical runs was [redacted] and the inter-assay %CV for QC ranged from [redacted]. There were 8 repeat samples out of 1380 analyzed samples due to inadequate chromatography, or unacceptable internal standard response. These repeats did not have significant impact on conclusion of the study.

b(4)

PHARMACOKINETICS

Statistical Methods: A sample size of 24 was recommended to meet the 80 – 125% confidence interval limits with a statistical power of at least 80% if the expected Cmax and AUC_I ratio were to fall between 92.5 and 107.5%. The pharmacokinetic parameters reported were C_{max}, $AUC_{...}$, AUC_I, $AUC_{I...}$, K_{el}, T_{max}, and $T_{1/2el}$.

Statistical and PK analyses were performed using Kinetic, version 8.00.007, an application developed at [redacted] and SAS version [redacted], [redacted] b(4)

All PK parameters were analyzed by the analysis of variance (ANOVA) in which treatment, sequence, period and period-by-treatment interaction as well as the left-over interaction terms between the three factors were modeled as fixed effects. The relative geometric mean and the 90% confidence interval of the relative geometric mean of C_{max}, AUC_{∞}, and AUC_T of the Test to each Reference products were calculated for the assessment of bioequivalence.

Results:

Twenty-three subjects received all three treatments. One subject completed syrup treatment only because she withdrew her consent for personal reasons before dosing of period 2. Therefore, 23 subjects were analyzed and included in the statistical analysis. The summary of the pharmacokinetic parameters for prednisolone and the results of bioequivalence testing are given in the following tables.

Table 8. Summary of Main Study Results Prednisolone 5 mg/5 mL Suspension vs Syrup

PARAMETER	TEST		REFERENCE-1		t (value)	p
	MEAN	C.V.	MEAN	C.V.		
C_{max} (ng/mL)	160.90	15.8	179.54	17.6	-4.25	<0.001
ln (C_{max}) (ng/mL)	5.0683	3.2	5.1755	3.4	-4.43	<0.001
T_{max} (hours)	1.33	41.5	0.75	29.1	5.82	<0.001
AUC_T (ng·h/mL)	821.77	20.2	791.39	19.6	2.45	<0.05
ln (AUC_T) (ng·h/mL)	6.6920	3.0	6.6554	2.9	2.53	<0.05
AUC_∞ (ng·h/mL)	852.26	19.6	825.22	19.0	2.21	<0.05
ln (AUC_∞) (ng·h/mL)	6.7293	2.9	6.6982	2.9	2.27	<0.05
$AUC_{T/\infty}$ (%)	96.34	1.2	95.82	1.3	2.16	<0.05
K_{el} ($hour^{-1}$)	0.2681	13.4	0.2628	9.9	1.05	N.S.
$T_{½el}$ (hours)	2.63	12.6	2.66	9.5	-0.72	N.S.

For T_{max}, the median is presented and the statistical analysis is based on ranks.
N.S.= Not Significant (p> 0.05)

Table 9. Comparison of Results with Standards for Bioequivalence Prednisolone 5 mg/5 mL Suspension vs Syrup

PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE-1		LOWER	UPPER
C_{max}	157.85	175.70	89.84	86.25	93.58
AUC_T	798.39	768.83	103.84	101.27	106.48
AUC_∞	828.90	802.53	103.29	100.84	105.80

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Best Possible Copy

Table 10. Summary of Main Study Results Prednisolone 5 mg/5 mL Suspension vs 1 x 5 mg Tablet

PARAMETER	TEST		REFERENCE-2		t (value)	p
	MEAN	C.V.	MEAN	C.V.		
C_{max} (ng/mL)	160.90	15.8	176.27	18.7	-3.47	<0.01
ln (C_{max}) (ng/mL)	5.0683	3.2	5.1561	3.5	-3.60	<0.001
T_{max} (hours)	1.33	41.5	1.00	33.2	0.83	N.S.
AUC_T (ng·h/mL)	821.77	20.2	812.50	17.7	0.68	N.S.
ln (AUC_T) (ng·h/mL)	6.6920	3.0	6.6855	2.6	0.39	N.S.
AUC_∞ (ng·h/mL)	852.26	19.6	846.62	17.1	0.40	N.S.
ln (AUC_∞) (ng·h/mL)	6.7293	2.9	6.7275	2.5	0.08	N.S.
$AUC_{T/\infty}$ (%)	96.34	1.2	95.89	1.3	1.91	N.S.
K_{el} (hour^{-1})	0.2681	13.4	0.2627	9.8	1.11	N.S.
$T_{1/2el}$ (hours)	2.63	12.6	2.66	10.0	-0.81	N.S.

For T_{max}, the median is presented and the statistical analysis is based on ranks.
N.S.= Not Significant ($p > 0.05$)

Table 11. Comparison of Results with Standards for Bioequivalence Prednisolone 5 mg/5 mL Suspension vs 1 x 5 mg Tablet

PARAMETER	GEOMETRIC LS MEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST	REFERENCE-2		LOWER	UPPER
C_{max}	157.85	172.23	91.65	87.99	95.47
AUC_T	798.39	793.73	100.59	98.09	103.14
AUC_∞	828.90	827.99	100.11	97.73	102.54

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Figure 1. Linear Profile of the Mean

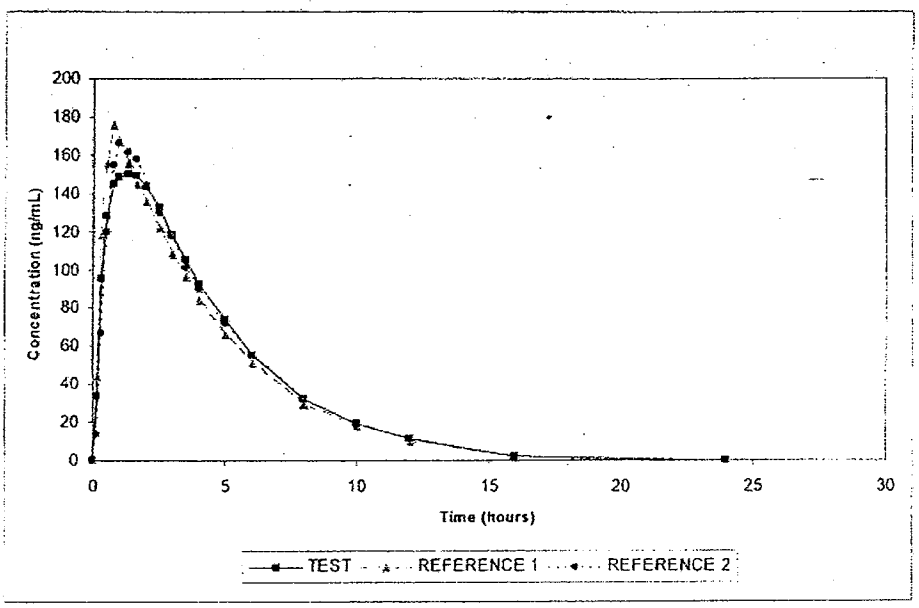
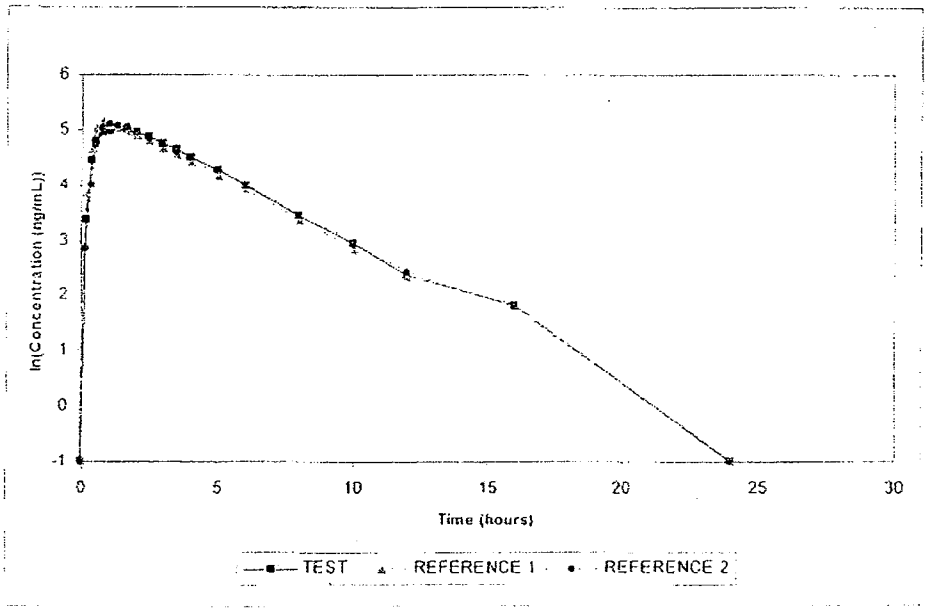


Figure 2. Logarithmic Profile of the Mean



SAFETY ASSESSMENT: Ten out of 24 subjects participating in the trial reported adverse events throughout the study. The intensity of the events ranged from mild to moderate. Similar number of subjects reported the AEs after each treatment (6 for Test, 5 for Reference B, and 7 for Reference C). Overall, the tolerability of the study drug products was acceptable.

CONCLUSION:

- The test product of Prednisolone Acetate Nonspil 5 mg/5 mL suspension is bioequivalent to the reference products, PrednisoLONE USP 5 mg 5 mL syrup [redacted] and Prednisolone USP 5 mg tablets [redacted] under fasted condition.

b(4)

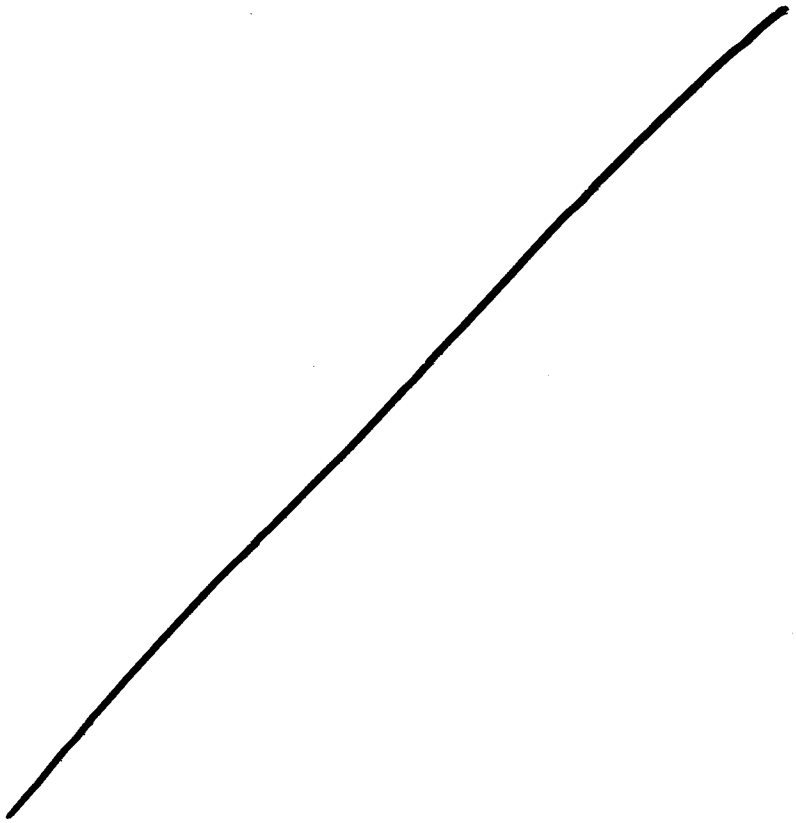
- There were no significant safety issues in each treatment of Prednisolone suspension, syrup, and tablets.

4.2.4 Analytical Method Validation

Validation of Method PEN-V4-320 (R3), "Validation of a HPLC Method Using MS Detection for the Determination of Prednisolone in Human Plasma" was conducted at the following site:

b(4)

An adequately validated HPLC/MS method was established to analyze the human plasma concentration of prednisolone. The following tables summarize the analytical method validation:



b(4)

4.3 OCP FILING/REVIEW FORM

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	**22-067**	**Brand Name**	**FLOPRED**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Prednisolone Acetate Oral Suspension**
Medical Division	**DAARP**	**Drug Class**	
OCP Reviewer	**Sally Y. Choe**		
Indication(s)	**Treatment of endocrine disorders; rheumatic disorders; [redacted] dermatologic diseases; allergic states; ophthalmic diseases; respiratory diseases; hematologic disorders; neoplastic diseases; gastrointestinal diseases: [redacted]**		
OCP Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Oral Suspension**
		Dosing Regimen	**5-60 mg/day**
Date of Submission	**8/11/2006**	**Route of Administration**	**oral**
Estimated Due Date of OCPB Review	**4/17/2007**	**Sponsor**	**Taro Pharmaceuticals U.S.A., Inc.**
PDUFA Due Date	**6/14/2007**	**Priority Classification**	**S**
Division Due Date	**6/1/2007**		

b(4)

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				

Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	3	3	
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				

Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3	3	

Filability and QBR comments		
	"X" if yes	**Comments**
Application fileable?	X	N/A
Comments sent to firm?		
QBR questions (key issues to be considered)	**Is the efficacy of new formulation of prednisolone, oral suspension acceptable based on 3 bioequivalence studies?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sally Choe
5/23/2007 08:22:56 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
5/23/2007 08:44:29 AM
BIOPHARMACEUTICS