CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40183

BIOEQUIVALENCY REVIEW(S)

JUL 1 1996

Methylprednisolone
4 mg Tablet
ANDA #40-183
Reviewer: Moheb H. Makary
WP 40183SD.296

Vintage Pharmaceuticals, Inc.
Charlotte, NC.
Submission Date:
February 29, 1996
June 6, 1996

Review of a Bioequivalence Study and Dissolution Data

I. Objective:

The objective of this study was to compare the plasma levels of Methylprednisolone, after administration of single dose of 4X4 mg Tablets of the test formulation (Vintage's Methylprednisolone Tablet, 4 mg) with that of Upjohn reference product (Medrol[R] Tablet, 4 mg) under fasting conditions. Dissolution profiles comparing Vintage's Methylprednisolone 4 mg tablets and Medrol® 4 mg tablets were submitted.

II. Introduction:

Methylprednisolone is a synthetic glucocorticoid, used principally as anti-inflammatory or immunosuppressant agent. It is indicated in endocrine and rheumatic disorders, collagen and dermatological diseases, allergic states, ophthalmic and respiratory diseases, hematological disorders, neoplastic diseases, edematous states, gastrointestinal diseases and multiple sclerosis, tuberculosis meningitis and trichinosis. It is readily absorbed from the gastrointestinal tract with peak plasma levels cccurring at 1-2 hours. The plasma half-life is about 3-4 hours.

Methylprednisolone is available commercially as 2 mg, 4 mg, 8 mg, 16 mg, 24 mg and 32 mg tablets. The innovator products are Medrol[R] tablets manufactured by the Upjohn Company.

III. Single Dose Bioequivalence Study #9528045B Under Fasting conditions:

Study site:

Sponsor: Vintage Pharmaceuticals, Inc.
Charlotte, NC.

Study design: A single-dose, randomized, two-treatment, two-period, two-sequence crossover design.

Subjects: Twenty-six healthy male volunteers were enrolled in the study. Twenty-five subjects

were dosed period I, and 24 subjects successfully completed the entire clinical portion of the study. Subject #4 was withdrawn from the study prior to dosing in period I because of a vasovagal response to the pre-dose blood sample collection. He did not receive any study drug. Subject #11 was withdrawn from the study prior to dosing in period II due to a positive urine drug screen. He received one dose of the reference treatment.

Selection criteria: Selection criteria include male volunteers between the age of 18 and 44 years with physical examination and medical history within normal limits, body weight within ± 15% of ideal body weight (Metropolitan Life Insurance Bulletin, 1983), and normal electrocardiogram. Physical exam, ECG and laboratory tests were conducted within 2 weeks of the study.

Laboratory tests: Blood chemistry, urine analysis, liver, HIV and kidney function tests were performed within 2 weeks of the study. Laboratory evaluations were not exceeded 10% of normal limits.

Exclusion criteria: Exclusion criteria were: ingestion of an investigational drug within four weeks prior to entry into the study; an acute illness or surgery during the four weeks prior to entry into the study; history of adverse reactions or allergy to methylprednisolone or Medrol; presence of significant renal, cardiac, hematopoietic, neurological, pulmonary or gastrointestinal pathology; ingestion of alcoholic beverage or caffeine or xanthine-containing food or beverages within 48 hours prior to start of the study.

Dose and treatment: All subjects completed an overnight fast. No meals were served within 4 hours of any of the following treatments:

A. Test product: 4 x 4 mg Methylprednisolone Tablets (Vintage), lot #069045, lot size tablets, content uniformity % (CV=1.8%), potency %.

B. Reference product:
4 x 4 mg Medrol[R] Tablets (Upjohn), lot #304XD, Exp. 12/99, content uniformity % (CV=2.6%) , potency %.

Washout period:	One week
Food and fluid intake:	Subjects fasted for ten hours prior to dosing. Lunch was served four hours after dosing. Water (240 mL) was given with the dose. Water intake was not permitted from 1 hour before and after dosing except for water (240 mL) administered with the dose.
Blood samples:	Blood samples were collected at 0 (pre-dose), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 15, and 18 hours. The plasma samples were stored frozen at -20°C until transfer to the laboratory for analysis.
Safety Evaluations:	Blood pressure and heart rate were measured prior to dosing, at scheduled intervals after dosing and at the discretion of the investigators.

Analytical Methodology

Statistical Analysis

Statistical analysis was performed on methylprednisolone data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The data analyzed by ANOVA were also performed for plasma drug concentrations at each sampling time. The 90% confidence intervals using the two one-sided t test method were calculated for AUC(0-t), AUCinf and Cmax.

IV. In Vivo Results:

Twenty-six healthy male subjects were entered into the study and twenty-four (6 Black and 18 Caucasian) subjects successfully completed the study.
Four adverse events reported in three of twenty-four subjects dosed are tiredness (3) and sleepiness (1). There were no serious adverse events or any events which required terminating any subject from the study.

The plasma levels and pharmacokinetic parameters for methyprednisolone in twenty-four (N=24) are summarized below:

Table I

Mean Plasma Methylprednisolone Concentrations and Pharmacokinetic Parameters Following a Single Dose of 4x4mg Methylprednisolone (4 Tablets) Under Fasting Conditions
(N=24)

Time hr	Vintage Test Product Lot#069045 ng/mL (CV)	Upjohn Reference Product Lot#304XD ng/mL (CV)
0	0.00	0.00
0.33	13.20 (97)	9.72 (148)
0.67	51.77 (57)	53.01 (68)
1	79.07 (38)	86.69 (39)
1.50	99.50 (29)	108.42 (25)
2	104.86 (22)	115.08 (21)
2.5	103.98 (23)	109.93 (20)
3	97.43 (27)	100.48 (20)
4	78.55 (33)	78.60 (25)
5	56.77 (40)	58.66 (39)
6	41.80 (46)	43.30 (44)
8	23.35 (55)	23.69 (56)
12	5.39 (131)	6.43 (126)
15	1.12 (284)	1.12 (360)
18	0.27 (490)	0.41 (480)

	Mean (CV)	Mean (CV)	90% CI
AUC(0-t) ng.hr/mL	552.06(36.5)	581.17(30.7)	
AUCinf ng.hr/mL	587.31(34.1)	614.02(29.2)	
CMAX (ng/mL)	113.44(23.0)	123.64(17.8)	
Kel (1/hr)	2.08	1.96	
Half (hr)	2.20	2.24	
Tmax(hr)	0.32	3.50	
LnAUC(0-t)			88-98%
LnAUCi			90-99%
LnCmax			86-96%

1. The methylprednisolone plasma levels peaked at 2 hours for both the test and reference products and were similar with each other. There were no statistically significant differences between the plasma methylprednisolone levels at any of sampling time points except for the two hour time point.

2. The data demonstrates that there are statistically significant differences for methylprednisolone between the test and the reference products for AUC(0-t), AUCi and Cmax. Differences from the least squares reference means of -5%, -4.3% and -8.2% for metylprednisolone AUC(0-t), AUCi and Cmax, respectively, were observed. The 90% confidence intervals for each of the above parameter are within the acceptable range of %. The reviewer's calculations are same as those submitted by the firm.

V. Formulation:

Vintage's formulation for its Metylprednisolone 4 mg Tablets is shown below:

Ingredient	4 mg Tablet MG Per Tablet
Metylprednisolone, USP	
Microcrystalline Cellulose, USP	
Sodium Starch Glycolate, NF	
Magnesium Stearate, NF	
Total	

VI. In Vitro Dissolution Testing

Method: USP 23 apparatus 2 at 50 rpm
Medium: 900 mL of water
Sampling Time: 5, 10, 20 and 30 minutes
Number of Tablets: 12
Test Products: Vintage's Methylprednisolone Tablets 4 mg, lot #069045
Reference Products: Upjohn's Medrol Tablets 4 mg, lot #304XD

The dissolution testing results are presented in Table II.

VII. Comments:

1. For Methylprednisolone, the firm's *in vivo* bioequivalence study under fasting conditions is acceptable. The test product is similar in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of % under fasting conditions.

2. The firm's *in vitro* dissolution testing for its Methylprednisolone, 4 mg tablets is acceptable.

VIII. Recommendations

1. The single-dose bioequivalence study under fasting conditions conducted by Vintage Pharmaceuticals, Inc., on its Methylprednisolone 4 mg Tablet, lot #069045, comparing it to Medrol[R] 4 mg Tablet, manufactured by Upjohn, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Vintage's Methylprednisolone Tablet, 4 mg is bioequivalent to the reference product, Medrol[R] Tablet, 4 mg, manufactured by Upjohn.

2. The dissolution testing conducted by the firm on its Methyprednisolone Tablets 4 mg, lot #069045, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

> NLT % of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE _____ Date: 6/27/96

Concur: /S/ Date: 7/1/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

Table II. In Vitro Dissolution Testing

Drug (Generic Name): Methylprednisolone
Dose Strength: 4 mg
ANDA No.: 40-183
Firm: Vintage Pharmaceuticals, Inc.
Submission Date: February 29, 1996
File Name: 40183SD.296

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of Water
Specifications: NLT % in 30
Reference Drug: Medrol
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 069045 Strength(mg) 4 mg			Reference Product Lot # 304XD Strength(mg) 4 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	76.5		11.5	58.1		20.8
10	89.7		4.2	81.9		16.2
20	95.8		3.9	99.5		7.2
30	94.0		6.7	102.3		4.4

STUDY NO. 9528045B

LEAST-SQUARES MEAN METHYLPREDNISOLONE PLASMA CONCENTRATIONS (N=24)