CENTER FOR DRUG EVALUATION AND RESEARCH

75-117

APPLICATION NUMBER:

BIOEQUIVALENCE

Prednisolone Sodium Phosphate
Oral Solution
20.2 mg/5 mL (equivalent to
15 mg/5 mL Prednisolone)
ANDA #75-117
Reviewer: Lin-Whei Chuang

Ascent Pediatrics, Inc.
Wilmington, MA

Submission Date:
September 18, 1998
December 11, 1998
December 14, 1998

Review of a Major amendment Containing a Bioavailability Study Report for Oral Solutions

Background:

The firm originally requested a waiver of *in vivo* bioequivalence requirements for the test drug product. It was denied (see review of 7/1/98) because:

1. The test formulation contains certain inactive ingredients which either is not included in the approved drug products (maltitol), or whose concentration in the proposed product exceeds that found in drug product approved for the same dosage form (sodium benzoate, monoammonium glycyrrhizinate, or fructose).

2. The Division is unable to conclude that differences in inactive ingredients discussed above will not significantly affect the absorption of the active moiety, prednisolone [Per 21 CFR 320.22(b)(3)(iii)].

In the present submission, the firm is providing a bioequivalence study report to demonstrate bioequivalence among the following four formulations:

1. Ascent Pediatrics (Orapred™) 15 mg/5 mL prednisolone sodium phosphate, formulation #F603 with maltitol.
2. Ascent Pediatrics (Orapred™) 15 mg/5 mL prednisolone sodium phosphate, formulation #F605 with 0% maltitol.
3. Medeva (Pediapred®) 5 mg/5 mL prednisolone sodium phosphate oral solution.
4. Muro (Prelone®) 15 mg/5 mL prednisolone syrup.

Formulation #3 is the reference listed drug, #4 is an approved formulation through ANDA #89081. The new strength is based on a ANDA-suitability petition filed by on 7/14/87 and approved on 11/4/87.

Prednisolone is rapidly and well absorbed following oral administration. Its kinetics are nonlinear due to its nonlinear plasma protein binding (70-90%). It is metabolized in liver and excreted in urine as sulfate and glucuronide conjugates. The reported Cmax, Tmax, and Thalf after oral dosing range of 10-40 mg are 391-585 ng/mL, 0.9-1.5 hours, and 2.7 hours, respectively.

Bioavailability Study under Fasting Conditions:

The objective of this study was to compare the single-dose bioavailability of two formulations of the firm's prednisolone sodium phosphate, one formulation of Medeva's Pediapred®, and one formulation of Muro's Prelone®, under fasting conditions.

The clinical study was conducted at the Clinical Research Center of in Cincinnati, Ohio during 6/6-8, 13-15, 20-22, & 27-29/98 by S. Wason, M.D., the principal investigator. The analytical study was conducted at the Analytical Division c

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The design was a randomized, 4-sequence, 4-way crossover in healthy subjects under fasting conditions. The study protocol (dated 5/7/98) was approved by Research Consultants' Review Committee on 5/18/98.

Twenty-four (24) male and female subjects were recruited. The were judged healthy according to the inclusion and exclusion criteria on pages 41-42, Vol. 4.1, of the submission. They were instructed of the prohibitions listed on pages 42-43, Vol. 4.1, of the submission (including not to take corticosteroids for 30 days preceding the study, not to use oral contraceptives for female subjects, and no immunization procedure from 2 weeks before to 2 weeks after the study).

After an overnight fast, in mornings of 6/7, 6/14, 6/21, & 6/28/98, each subjects received one of the following four treatments according the randomly assigned sequences:

Treatment A - 5 mL of Ascent Pediatrics (Orapred™)
15 mg/5 mL prednisolone sodium phosphate,
formulation #F603 with maltitol,
lot #6EX29C, potency , batch size

Treatment B - 5 mL of Ascent Pediatrics (Orapred™)
15 mg/5 mL prednisolone sodium phosphate,
formulation #F605 with 0% maltitol,
lot #7EX1308, potency batch size

Treatment C - 15 mL of Medeva (Pediapred®) 5 mg/5 mL
prednisolone sodium phosphate oral solution,
lot #70703, potency expires 07/99.

Treatment D - 5 mL of Muro (Prelone®) 15 mg/5 mL
prednisolone syrup, lot #81001, expires 01/2001.

Sequence ABCD: Subjects #2, 7, 11, 17, 18, 21
Sequence BDAC: Subjects #6, 8, 10, 16, 19, 20
Sequence CADB: Subjects #1, 9, 12, 13, 22, 23
Sequence DCBA: Subjects #3, 4, 5, 14, 15, 24

Each treatment was taken with 240 mL of water. Subjects continued to fast for 4 hours and remained ambulatory for 1 hour after dosing. They were housed at the clinical facility from the evening before dosing until after the 24-hour blood draw.

Blood samples were collected into Vacutainers containing heparin at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dosing. Plasma samples were stored at -12°C or lower and shipped to the analytical site on during 6/30-7/2/98.

Analytical Method:

A total of 1564 plasma samples, stored in dried ice, were received at the analytical site during 6/30-7/2/98. Prednisolone concentrations in plasma samples were determined using with detection. The internal standard was pre-study validation data are presented below in Table 1:

Table 1: Pre-Study Validation for Analysis of Prednisolone	
Parameter	
Sensitivity/LLOQ (ng/mL)	0.94
Quality Control Conc.(ng/mL) (Lo, Med, Hi, & LLOQ)	2.82, 140.82, 328.58, 0.94
Linear Range (ng/mL)	0.94 - 470.81
Correlation Coefficient	≥0.9939
Intra-run Precision (%CV)	1.9 - 15.6
Intra-run Accuracy (%Actual)	80.5 - 97.4
Inter-run Precision (%CV)	1.6 - 11.8
Inter-run Accuracy (%CV)	94.4 - 105.9
Selectivity	no interference
Stability of Spiked Plasma Samples a) Plasma Sample- 11.7 Hr @ 20° b) Plasma Sample- 3 Freeze-Thaw Cycles c) Plasma Sample- @ -22° C for 86 days	% (ng/mL) 95.2 103.4 (2.82) (328.58) 103.1 97.9 (2.82) (328.58) 107.6 92.4 (2.82-2.99) (328.58-349.30)
Percent Recovery of QC samples and internal standard (1000 ng/mL)	% (ng/mL) 88.58 84.46 82.55 (2.82) (40.82) (328.58) 86.00 (1000)

For the analysis of prednisolone in study samples, the firm conducted 25 standard curves, each with duplicates of 3 levels of QC samples. Validation of these data are presented below in Table 2:

Table 2: During-Study Validation for Analysis of Prednisolone	
Parameter	
Sensitivity/LLOQ (ng/mL)	1.01
Quality Control Conc.(ng/mL) (Lo, Med, & Hi)	3.01, 150.60, 351.40
Linear Range (ng/mL)	1.01 - 504.50
Correlation Coefficient	≥0.9979
Precision (%CV) of QC Samples	5.4 - 7.0
Accuracy of QC Samples (%Actual)	92.5 - 94.4
Precision (%CV) of Standards	4.0 - 9.1
Accuracy of Standards (%Actual)	93.9 - 108.7

Comment on the Analytical Method:

The analytical method and validation data are acceptable.

Results:

Of the 24 subjects enrolled in the study, 23 completed the study. Subject #21 withdrew from the study for personal reasons before check-in of period 2.

No major protocol deviation were reported. However, among the 17 adverse events reported, 14 occurred after treatment A (the test formulation), 1 after treatment B (test formulation without maltitol), and 2 after treatment D. The nature of these complaints were nausea, headache, dizziness, stomach cramps, tingling all over,, weakness, hot feeling, and vomiting. The 14 adverse events occurred after treatment A were reported by subjects #6 and #21, however only 6 of them (headache, stomach cramps, nausea or vomiting) were considered possibly related the test formulation and no action was required for these events.

The mean plasma concentrations and pharmacokinetic parameters of prednisolone at each sampling time point after all 4 treatments are presented in Figure 1 and Tables 3-4.

TABLE 3: MEAN PLASMA PREDNISOLONE LEVELS (NG/ML) FOR TEST (A) AND REFERENCE (C) PRODUCTS AND OTHER FORMULATIONS (B & D)
-- SINGLE 15 MG DOSE UNDER FASTING CONDITIONS, N=23 --

	TRT A	SD	TRT B	SD	TRT C	SD	TRT D	SD	A/C
TIME HR									
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	...
0.25	173.88	102.52	183.46	92.04	164.19	71.97	236.74	88.89	1.06
0.5	302.08	73.10	316.22	95.24	304.81	68.72	339.28	47.83	0.99
0.75	315.36	45.01	331.29	60.55	323.85	61.87	337.73	47.70	0.97
1	301.33	39.81	318.72	51.17	327.13	58.49	327.22	50.28	0.92
1.5	283.26	50.13	289.46	45.51	292.43	47.97	292.94	47.79	0.97
2	255.21	38.90	266.99	51.94	262.09	42.36	268.46	44.36	0.97
2.5	234.37	39.30	239.56	43.79	241.89	36.90	244.56	32.26	0.97
3	218.37	38.93	222.45	32.11	218.37	41.46	227.08	34.20	1.00
4	172.31	29.45	185.49	27.01	180.99	35.92	189.43	33.99	0.95
5	142.61	25.32	147.40	27.23	148.61	24.07	149.85	27.97	0.96
6	113.36	30.02	112.72	25.77	109.87	23.52	111.55	27.53	1.03
8	62.43	15.94	68.15	21.92	66.75	16.48	62.98	15.04	0.94
10	39.91	13.03	43.28	15.17	39.74	13.32	40.16	11.24	1.00
12	24.03	9.99	25.35	8.55	22.92	8.85	23.25	8.56	1.05
16	8.83	4.09	9.25	4.85	8.58	3.44	8.67	3.94	1.03
24	1.34	1.19	1.47	1.26	1.38	0.93	1.35	1.06	0.97

TABLE 4: MEAN PHARMACOKINETIC PARAMETERS FOR TEST (A) AND REFERENCE (C) PRODUCTS AND OTHER FORMULATIONS (B & D)
-- SINGLE 15 MG DOSE UNDER FASTING CONDITIONS, N=23 --

	TRT A	SD	TRT B	SD	TRT C	SD	TRT D	SD	A/C
PARAMETER									
AUCI	1685.48	315.93	1760.00	321.58	1721.78	313.18	1768.83	298.12	0.98
AUCT	1672.83	314.42	1749.13	319.50	1712.35	311.99	1759.09	296.65	0.98
CMAX	339.78	49.43	361.77	51.54	349.55	53.35	361.53	38.88	0.97
KE	0.24	0.03	0.24	0.03	0.24	0.03	0.25	0.03	1.00
LAUCI	1662.52	---	1736.77	---	1698.27	---	1747.56	---	0.98
LAUCT	1649.85	---	1725.87	---	1688.82	---	1737.81	---	0.98
LCMAX	336.51	---	358.52	---	345.99	---	359.61	---	0.97
THALF	2.90	0.32	2.90	0.32	2.88	0.28	2.84	0.30	1.01
TMAX	0.76	0.24	0.77	0.35	0.91	0.39	0.70	0.28	0.83

The ratios of test (treatment A) to reference (treatment C) products of 3 major pharmacokinetic parameters are presented in Table 5.

TABLE 5: RATIOS OF TEST TO REFERENCE OF THREE MAJOR PHARMACOKINETIC PARAMETERS
--- SINGLE 15 MG DOSE UNDER FASTING CONDITION ---

SUB	SE	AUCT	AUCI	CMAX
1	3	1.00	1.00	0.89
2	1	0.99	0.99	0.96
3	4	1.02	1.02	1.09
4	4	0.95	0.95	0.98
5	4	1.01	1.01	1.01
6	2	0.82	0.82	0.77
7	1	0.97	0.97	1.13
8	2	0.94	0.94	0.94
9	3	0.99	0.99	1.14
10	2	1.07	1.06	0.94
11	1	0.89	0.89	0.70
12	3	1.04	1.04	1.05
13	3	0.92	0.92	1.10
14	4	1.03	1.03	1.01
15	4	1.04	1.04	0.97
16	2	0.93	0.93	0.99
17	1	1.02	1.02	0.85
18	1	1.06	1.06	1.08
19	2	0.74	0.75	0.85
20	2	0.96	0.96	0.83
22	3	0.94	0.95	1.01
23	3	1.08	1.08	1.05
24	4	1.16	1.16	1.18

Analysis of Variance was conducted on the non-transformed and log-transformed pharmacokinetic parameters with a model including subjects within sequence, period, and treatment as

factors. A 5% level of significance was used. Each ANOVA included calculation of least-squares means and 90% confidence intervals for the difference between test and reference drugs and are presented below in Table 6:

Table 6: Least-Squares Means and 90% Confidence Intervals for Test and Reference

	LSM:TRT A	LSM:TRT B	LSM:TRT C	LSM:TRT D	RATIO A/C	90% CI OF TRT A/C
PARAMETER						
AUCI	1679.09	1754.69	1719.12	1769.07	0.98	94.91 -- 100.43
AUCT	1666.64	1743.86	1709.81	1759.49	0.97	94.67 -- 100.28
CMAX	338.62	360.45	349.15	361.39	0.97	92.78 -- 101.18
LAUCI	1656.84	1731.96	1696.21	1748.34	0.98	95.06 -- 100.37
LAUCT	1644.38	1721.10	1686.89	1738.75	0.97	94.82 -- 100.21
LCMAX	335.40	357.24	345.65	359.50	0.97	93.16 -- 101.07

When the factor of first-degree carryover was added to the ANOVA model, significant residual effects were detected for the AUCs. The 90% confidence interval obtained with the residual effect in the model are presented below in Table 7:

Table 7: Least-Squares Means and 90% Confidence Intervals for Test and Reference with Residual Effects

PARAMETER	90% CI OF TRT A/C
LAUCI	96.35 -- 101.72
LAUCT	96.10 -- 101.56
LCMAX	93.34 -- 101.75

Comments on the Clinical Study:

1. It was noted that subjects #6 & 21 experienced headache, stomach cramps, nausea, and vomiting after administration of treatment A (test formulation), while none occurred after the administration of treatment C (reference formulation). It was reported that relationship of these events to the study drug could not be excluded. However, no action was needed for these adverse events.

2. The pharmacokinetic parameters and 90% confidence intervals presented above were calculated by the reviewer. They are almost identical to those submitted by the firm. The 90% confidence intervals of all log-transformed pharmacokinetic parameters are all within the acceptable range of 80-125%.

3. The analysis of data from treatments A and B indicate that these formulation A and B are also bioequivalent.

Formulations of Test Products :

	Formula #F-603 Lot #6EX29	Formula #F605 Lot 7EX13
Ingredient	Amount (mg/5 mL)	
Sorbitol	272	272
Maltitol		
Povidone		
Alcohol		
Monoammonium Glycyrrhizinate		
Glycerin		
Flavor		
Sodium Benzoate		
Prednisolone Sodium Phosphate		
Fructose	2481	
Water		

Recommendation:

The *in vivo* bioavailability study conducted by Ascent Pediatrics, Inc. on its Prednisolone Sodium Phosphate Oral Solution, 15 mg of prednisolone/5 mL, lot #6EX29C and lot #7EX1308, comparing them to Pediapred® (prednisolone sodium phosphate oral solution, 5 mg of prednisolone/5 mL), lot #70703, manufactured by Medeva, and Prelone® (prednisolone oral syrup), 15 mg of prednisolone/5 mL, lot #81001, manufactured by Muro, has been found acceptable by the Division of Bioequivalence.

Lin-Whei Chuang 12/14/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch 1

RD INITIALED YHUANG
FT INITIALED YHUANG 12/16/98

Concur: Dale P. Conner Date: 12/30/98
Dale Conner, Pharm. D.
Director, Division of Bioequivalence