CENTER FOR DRUG EVALUATION AND RESEARCH

75-117

APPLICATION NUMBER:

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
75-117	Neeru Takiar	November 01, 2000

DRUG PRODUCT:
Orapred™ (Prednisolone Sodium Phosphate Oral Solution)

FIRM:
Ascent Pediatrics, Inc.

DOSAGE FORM:	STRENGTH:
Solution	20.2 mg/5 mL (EQ to 15 mg base/5 mL)

cGMP:
EER was found acceptable for all the establishments on July 19, 2000.

BIO:
Reviewed by L.Chuang and found satisfactory on March 16, 1999 and signed off 3/18/99.
Flavoring found satisfactory on October 27, 2000 and signed off 10/31/00.

VALIDATION *(Description of dosage form same as firm's):*
Pending results. The method is acceptable in the CMC review section.

STABILITY:
The containers in the stability studies are identical to those in the container section.

LABELING:
Container, carton, and insert labeling acceptable by D. Catterson on March 22, 2000.

STERILIZATION VALIDATION *(If applicable)*:
Not applicable.

SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:
The bio batch (7EX13) size is

SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?)*:
Same as the bio batch.

PROPOSED PRODUCTION BATCH MANUFACTURING PROCESS THE SAME?
The proposed production batches is The manufacturing processes are identical, except the vessel size changes in the certain steps.

Signature of chemist:	Signature of supervisor:
Neeru B. Takiar Ntakiar 11/1/00	Dave Gill, Ph.D. DSGill 11-1-00

Prednisolone Sodium Phosphate Oral Solution 20.2 mg/5 mL (equivalent to 15 mg/5 mL Prednisolone)	Ascent Pediatrics, Inc. Wilmington, MA
ANDA #75-117	Submission Date:
Reviewer: Lin-Whei Chuang	January 18, 1999

Review of an Amendment (Waiver Request)

Background:

The firm's original request (6/24/97) of a waiver of *in vivo* bioequivalence requirements for the test drug product with the old formulation (containing maltitol) was denied due to issues regarding inactive ingredients. The subsequent amendment (2/3/98) was found to be deficient and the waiver was again not granted. The firm then conducted a bioavailability study for the following formulations and results were submitted on 9/18/98:

A. Ascent Pediatrics (Orapred™) 15 mg/5 mL prednisolone sodium phosphate, formulation #F603 with **20% maltitol**.

B. Ascent Pediatrics (Orapred™) 15 mg/5 mL prednisolone sodium phosphate, formulation #F605 with **0% maltitol**.

C. Medeva (Pediapred®) 5 mg/5 mL prednisolone sodium phosphate oral solution.

D. Muro (Prelone®) 15 mg/5 mL prednisolone syrup.

Formulation C is the reference listed drug, formulation D is an approved formulation through ANDA #89081.

Results of the aforementioned bioavailability study was found to be acceptable by the Division of Bioequivalence since the 90% confidence intervals of all major pharmacokinetic parameters are within 80-125% when comparing formulations A to C.

In this present amendment, the firm submitted information to support a new formulation without maltitol which is the same formulation as formulation B used in the

bioavailability study except that the fructose concentration was reduced from 2978 mg/5 mL to 2481 mg/5 mL.

Review:

Results from the bioavailability study indicated that the 90% confidence intervals of all major pharmacokinetic parameters comparing the newly proposed formulation without maltitol (formulation B) to the reference listed drug (formulation C) are within 80-125% (Table1).

Table 1 Least-Squares Means and 90% Confidence Intervals for Test and Reference

	LSM:TRT A	LSM:TRT B	LSM:TRT C	LSM:TRT D	RATIO B/C	90% CI OF TRT B/C
PARAMETER						
AUCI	1679.09	1754.69	1719.12	1769.07	0.98	99.30 -- 104.83
AUCT	1666.64	1743.86	1709.81	1759.49	0.97	99.19 -- 104.80
CMAX	338.62	360.45	349.15	361.39	0.97	99.03 -- 107.44
LAUCI	1656.84	1731.96	1696.21	1748.34	0.98	99.37 -- 104.92
LAUCT	1644.38	1721.10	1686.89	1738.75	0.97	99.25 -- 104.89
LCMAX	335.40	357.24	345.65	359.50	0.97	99.22 -- 107.65

Because the bioavailability study conducted by the firm was a 4-period design, the factor of first-degree carryover was added to the ANOCA model; the 90% confidence intervals of pivotal pharmacokinetic parameters are still within the acceptable range of 80-125% (Table 2).

Table 2: 90% Confidence Intervals with Residual Effects

PARAMETER	90% CI OF TRT B/C
LAUCI	99.3 -- 104.8
LAUCT	99.2 -- 104.8
LCMAX	98.8 -- 107.6

Therefore the newly proposed formulation without maltitol is similarly bioavailable to the reference listed drug. The differences in the quantity and quality of inactive ingredients did not significantly affect the absorption of prednisolone.

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Ascent Pediatrics, Inc. demonstrates that the new formulation of prednisolone sodium phosphate oral solution, 20.2 mg mg/5 mL, falls under Section 320.22 (b)(3) of Bioavailability/Bioequivalence Regulations. Waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test oral solution formulation manufactured by Ascent Pediatrics, Inc. to be similarly bioavailable to Pediapred® oral solution, 5 mg of prednisolone/5 mL, marketed by Medeva.

Lin-Whei Chuang 3/16/99

Lin-Whei Chuang
Division of Bioequivalence
Review Branch 1

RD INITIALED YHUANG
FT INITIALED YHUANG 3/16/99

Concur: _____ Date: _____
Dale Conner, Pharm. D.
Director, Division of Bioequivalence

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

Ascent Pediatrics, Inc.
Wilminton, MA
Submission Date:
February 3, 1998

Review of an Amendment to a Waiver Request

This application is for the approval of a new concentration, 15 mg prednisolone equivalent/5 mL, which differs from the reference listed drug (Pediapred® oral liquid, 15 mg prednisolone equivalent/5 mL, marketed by Medeva Pharmaceuticals, Inc., and approved under NDA #19157 on 5/28/86). This is based on a ANDA-suitability petition filed by Fisons Corporation on 07/14/87 (docket #87P-0235/CP). The petition was approved by the Agency on 11/04/87.

The firm's request of a waiver of *in vivo* bioequivalence requirements for its prednisolone sodium phosphate oral liquid, 15 mg prednisolone equivalent/5 mL, based on 21 CFR 320.22 (b)(3) was denied due to 4 deficiencies. The firm's responses are reviewed below:

1. The formulation of the test product differs greatly from that of the reference listed drug.

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Contain Trade Secret, Commercial/Confidential Information and are not releasable.

2/3/98

Reviewer's Comment: The data of physical and chemical properties will be reviewed by the Chemistry Division of the Office.

Deficiencies:

1. The test formulation contains certain inactive ingredients which either are not included in the approved drug products (maltitol), or whose concentrations in the proposed product exceed that found in drug product approved for the same dosage form and route of administration (sodium benzoate, monoammonium glycyrrhizinate, and 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)].

   The argument made by the firm in reference to its application (ANDA is immaterial because the active ingredient is totally different.

Recommendations:

The Division of Bioequivalence has reviewed the information submitted by Ascent Pediatrics, Inc., and determined that the waiver for the firm's prednisolone sodium phosphate oral solution, 15 mg prednisolone equivalent/5 mL, can not be granted based on 21 CFR 320.22(b)(3) due to the above deficiencies.

The firm should be informed of the above deficiencies and recommendation.

Lin-Whei Chuang 6/25/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG _____ Date: 6/25/98

Concur: Dale P. Conner Date: 7/1/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

Prednisolone Sodium Phosphate (Orapred™)
Oral Solution
15 mg Prednisolone /5 mL
(20.2 mg Prednisolone Sodium Phosphate/5 mL)

Ascent Pediatrics, Inc.
Wilminton, MA

ANDA # 75-117
Reviewer: Lin-Whei Chuang

Submission Date:
June 24, 1997

Review of a Waiver Request

Background:

The firm is requesting a waiver of *in vivo* bioequivalence requirements for its prednisolone sodium phosphate oral liquid, 15 mg prednisolone equivalent/5 mL, based on 21 CFR 320.22 (b)(3). The product is indicated for various disorders and diseases, i.e., endocrine, rheumatic, or hematologic disorders; collagen, dermatologic, ophthalmic, respiratory, neoplastic or gastrointestinal diseases; and edematous states, nervous system, or other miscellaneous uses.

The reference listed drug is Pediapred® oral liquid, 5 mg prednisolone equivalent/5 mL, marketed by Medeva Pharmaceuticals, Inc., and approved under NDA #19157 on 5/28/86.

This application is for the approval of a **new concentration, 15 mg prednisolone equivalent/5 mL**, which differs from the reference listed drug. This is based on a ANDA-suitability petition filed by Fisons Corporation on 07/14/87 (docket #87P-0235/CP). The petition was approved by the Agency on 11/04/87.

Formulation Comparison: **(Not to be released through FOI)**

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Contain Trade Secret, Commercial/Confidential Information and are not releasable.

6/24/97

Agency's Inactive Ingredient Guide.

6.

7.

Deficiencies:

1. The formulation of the test product differs greatly from that of the reference listed drug.

2.

3.

administration."

4. The exact amount of fructose present in the test formulation is not reported.

5. The physical and chemical properties of the test product are not reported.

Recommendations:

The Division of Bioequivalence has reviewed the information submitted by Ascent Pediatrics, Inc., and determined that the waiver for the firm's prednisolone sodium phosphate oral solution, 6.7 mg/5 mL, can not be granted based on 21 CFR 320.22(b)(3) due to the above deficiencies.

The firm should be informed of the above deficiencies and recommendation.

Lin-Whei Chuang 12/3/97

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG Date: 12/3/97

Concur: Date: 12/9/97
Rabindra Patnaik, Ph.D.
~~Acting~~ for Director, Division of Bioequivalence

cc: 'Huang),