CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-067

SUMMARY REVIEW

Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Drug Products

Medical Officer Team Leader Memorandum

Date: May 3, 2007

To: File, NDA 22-067

From: Jeffrey Siegel, M.D.
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Drug Products

Re: NDA 22-067
Flo-Pred (Prednisolone oral suspension): 5 mg/5 mL and 15 mg/5 mL
Taro Pharmaceuticals U.S.A., Inc.

1. Introduction to Review

Taro Pharmaceuticals U.S.A. is submitting a new drug application (NDA) to market a new formulation of prednisolone – [redacted] 5 mg/5 mL and 15 mg/5 mL. The submission is a 505(b)(2) NDA that references efficacy and safety data for the previously approved prednisolone formulations. Bioequivalence to the reference prednisolone product is based on pharmacokinetic studies. This review will focus on the data supporting bioequivalence to the reference prednisolone product. b(4)

2. Chemistry, Manufacturing and Controls

2.1. General product quality considerations

The drug substance is prednisolone acetate, which is an adrenal corticosteroid. Prednisolone acetate is a white to almost white, odorless powder. It is practically insoluble in water. The drug products are prednisolone acetate oral suspension 0.097%, equivalent to 5 mg/g mL prednisolone base and 0.293%, equivalent to 15 mg/5 mL prednisolone base, with cherry flavor. The product was developed as [redacted] formulations. It does not require shaking to maintain product uniformity. b(4)

There were no unresolved CMC issues. The drug substance, prednisolone acetate, USP micronized was originally to be supplied by two manufacturers, [redacted] The was inadequate documentation to support the [redacted] source. The sponsor withdrew the [redacted] source from the application in an amendment dated 7/11/07. b(4)

2.2. Facilities review/inspection

The Office of Compliance provided an overall recommendation of acceptable on the proposed manufacturing and testing sites.

3. Clinical Pharmacology

Approval of [redacted] oral suspension is sought based on three bioequivalence studies comparing it to 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). b(4)

Study PEN-P5-319 compared a 15 mg of NonSpil oral suspension (15 mg/5 mL) to two reference products – syrup (15 mg/5 mL) and tablet (3x5 mg) – under fasted conditions. Study PEN-P5-320 compared a 15 mg dose of NonSpil oral suspension (15 mg/5 mL) to the same two reference products under fed conditions. Study PEN-P5-321 compared 5 mg doses of the 5 mg/5 mL NonSpil oral suspension to two reference products, prednisolone syrup (5 mg/5 mL) and tablet (1x5 mg). In the three studies (Table 1, copied from the review by Dr. Jim Witter), the 90% confidence interval around the means b(4)

of the Cmax and AUC for [redacted] suspensions were within 80-125% of the reference prednisolone tablets and syrup, thereby demonstrating bioequivalence. b(4)

Table 1: Results of bioavailability studies

Parameter	Study (fasted) PEN-P5-319				
	NonSpil 15 mg/5mL	Syrup 15 mg/5 mL	Tablet 5 mg x 3	Ratio (%) NonSpil vs. Syrup [90% C.I.]	Ratio (%) NonSpil vs. Tablet [90% C.I.]
Cmax a (ng/L)	298.20	345.00	308.72	86.44 [82.76-90.27]	96.59 [92.49-100.88]
AUC(0-t) a (ng*hr/L)	1770.09	1700.64	1760.79	104.08 [100.82-107.45]	100.53 [97.38-103.78]
AUC(0-∞) a (ng*hr/L)	1818.71	1745.80	1813.57	104.18 [100.96-107.49]	100.28 [97.19-103.47]
	Study (fed) PEN-P5-320				
	NonSpil 15 mg/5mL	Syrup 15 mg/5mL	Tablet 5 mg x 3	Ratio (%) NonSpil vs. Syrup [90% C.I.]	Ratio (%) NonSpil vs. Tablet [90% C.I.]
Cmax a (ng/L)	235.72	252.09	269.92	93.51 [90.13-97.01]	87.33 [84.23-90.54]
AUC(0-t) a (ng*hr/L)	1956.86	1818.90	1756.10	107.58 [103.45-111.89]	111.43 [107.22-115.81]
AUC(0-∞) a (ng*hr/L)	2023.74	1865.25	1804.51	108.50 [104.27-112.90]	112.15 [107.85-116.62]
	Study (fasted) PEN-P5-321				
	NonSpil 5 mg/5mL	Syrup 5 mg/5mL	Tablet 5 mg	Ratio (%) NonSpil vs. Syrup [90% C.I.]	Ratio (%) NonSpil vs. Tablet [90% C.I.]
Cmax a (ng/L)	157.85	175.70	172.23	89.84 [86.25-93.58]	91.65 [87.99-95.47]
AUC(0-t) a (ng*hr/L)	798.39	768.83	793.73	103.84 [101.27-106.48]	100.59 [98.09-103.14]
AUC(0-∞) a (ng*hr/L)	828.90	802.53	827.99	103.29 [100.84-105.80]	100.11 [97.93-102.54]

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The Clinical Pharmacology review team concluded that the applicant had demonstrated bioequivalence to the reference product.

4. Clinical

4.1. Efficacy and safety

No efficacy or safety data were submitted in this application. Evidence of efficacy and safety is based on the 505(b)2 reference to prednisolone, which was approved under the DESI process. The adverse events experienced by the normal volunteers in the bioavailability studies were reviewed in detail by the clinical reviewer. No safety concerns were raised in the review of these data.

5. Special populations

The sponsor sought a waiver of the requirement for pediatric studies. In 2005, the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550) consulted the Division of Pediatric Drug Development (DPDD, HFD-960) asking whether a new prednisolone product, Orapred, should be required to carry out pediatric studies under PREA. It was noted that there was a generic prednisolone product, Orapred, that was currently marketed. In their response DPDD stated that pediatric studies could be waived "because the already marketed formulations permit flexibility in dosing across the dosage range recommended for prednisolone in the pediatric population." Based on this assessment, a waiver of pediatric studies is appropriate for [redacted] as well b(4)

6. Conclusions and recommendations

This 505(b)2 application for [redacted] appropriately references approved prednisolone formulations for safety and efficacy. Three bioavailability studies demonstrate bioequivalence of [redacted] to the reference prednisolone products. b(4)

This NDA should be approved with appropriate changes to the proposed labeling.

APPEARS THIS WAY ON ORIGINAL

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/s/

Jeffrey N Siegel
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MEDICAL OFFICER