CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-959

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-959 SUPPL # HFD # 170

Trade Name ORAPRED ODT

Generic Name prednisolone sodium phosphate orally disintegratign tablets

Applicant Name BioMartin (Medicis)

Approval Date, If Known June 1, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Demonstration of bioequivalence of Orapred ODT to the reference listed drug product, Pediapred oral solution (NDA 19-157) is being relied upon for approval. There are no arguments from sponsor on this aspect.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form:
Title:
Date:

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Bob Rappaport
6/1/2006 11:12:22 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-959 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: August 1, 2005 **Action Date:** June 1, 2006

HFD 170

Trade and generic names/dosage form: ORAPRED ODT (prednisolone sodium phosphate orally disintegrating tablets)

Applicant: Medicis Pharmaceuticals **Therapeutic Class:** 3S

Indication(s) previously approved: (See below)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 60

Not rare in pediatrics	Not found or rare in pediatrics
Endocrine Disorders	
Adrenocortical insufficiency	Hypercalcemia associated w/ cancer
Congenital adrenal hyperplasia	
Non-suppurative thyroiditis	
Rheumatic Disorders	
Psoriatic arthritis	Ankylosing spondylitis
Rheumatoid arthritis*	Acute gouty arthritis
Acute & subacute bursitis (adolescents)	Epicondylitis
Acute nonspecific tenosynovitis	Dermatomyositis
Systemic lupus erythematosus	Sjögren's syndrome
	Relapsing polychondritis
Vasculitis	Polymyalgia rheumatica
Dermatologic Diseases	
Bullous dermatitis herpetiformis	Pemphigus
Severe erythema multiforme (Steven-Johnson syndrome)	
Exfoliative erythroderma	
Mycosis fungoides	
Allergic States*	
Seasonal allergic rhinitis	
Perennial allergic rhinitis	
Asthma	
Contact dermatitis	
Atopic dermatitis	

Serum sickness	
Drug hypersensitivity reactions	
Ophthalmic diseases	
Uveitis & ocular inflammatory conditions	Temporal arteritis
	Sympathetic Ophthalmia
Respiratory diseases	
Rulminating or disseminated pulmonary tuberculosis	Symptomatic sarcoidosis
Asthma (distinct from allergic asthma)	Idiopathic eosinophilic Pneumonias
Pneumocystis carinii pneumonia (PCP) associated w/ hypoxemia occurring in HIV+ individuals who are also under treatment w/ appropriate anti-PCP antibiotics	Hypersensitivity pneumonitis
	Idiopathic pulmonary fibrosis
	Chronic obstructive pulmonary disease
Hematologic disorders	
Idiopathic thrombocytopenia purpura**	Diamond-Blackfan anemia
Secondary thrombocytopenia	
Acquired (autoimmune) hemolytic anemia	
Pure red cell aplasia	
Neoplastic diseases	
Acute leukemia	
Aggressive lymphomas*	
Edemalous states	
To induce diuresis or remission of proteinuria in nephrotic syndrome in adults w/ lupus erythematosus and in adults and pediatric populations w/ idiopathic nephrotic syndrome, w/o uremia	
Gastrointestinal diseases	
Ulcerative colitis	
Regional enteritis	
Nervous system	
Multiple sclerosis	
Miscellaneous	
Tuberculosis (various forms)	
Trichinosis w/ neurologic or myocardial involvement	
Acute or chronic solid organ rejection	

* RLD label indicates that these indications are approved in both adult and pediatric patients.
** RLD label indicates "in adults," but this condition also occurs in pediatric patients.

With several exceptions, the indications listing under the following categories are considered **FULFILLED**:

- Allergic states
- Dermatologic disorder
- Edemalous states
- Endocrine disorders
- Gastrointestinal diseases
- Hematologic disorders
- Miscellaneous
- Neoplastic diseases
- Nervous systems
- Ophthalmic diseases
- Respiratory diseases
- Rheumatic disorders

With respect to the above-mentioned exceptions, the following indications are **WAIVED** either because the disease/condition does not occur in the pediatric population or there are too few children with disease/condition to study:

- Acute gouty arthritis
- Ankylosing spondylitis,
- Chronic obstructive pulmonary disease (COPD)
- Diamond-Blackfan anemia
- Epicondylitis, dermatomyositis
- Hypercalcemia associated with cancer
- Hypersensitivity pneumonitis
- Idiopathic eosinophilic pneumonias
- Idiopathic pulmonary fibrosis
- Pemphigus
- Relapsing polychondritis
- Sjörgen's syndrome
- Sympathetic ophthalmia
- Symptomatic sacoidosis
- Temporal arteritis

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-959
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Bob Rappaport
6/1/2006 11:17:03 AM

MEDICIS®

DEBARMENT CERTIFICATION

Orapred ODT™
10 mg, 15 mg, and 30 mg Prednisolone* Orally Disintegrating Tablets
(Equivalent to 13.44 mg, 20.16 mg, and 40.32 mg of Prednisolone Sodium Phosphate)

Certification Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. Section 335a(k)(1)].

Medicis Pharmaceutical Corp., and BioMarin Pharmaceutical Inc., certify that the services of any person debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act [21 U.S.C. Section 335a (a) or (b) were not and will be not used in any capacity in connection with this application.

R. Todd Plott, M.D.
Vice President,
Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

7/25/05
Date

Ruhi Ahmed, Ph.D.
BioMarin Pharmaceutical Inc.
Regulatory Agent

7/26/05
Date

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	June 1, 2006
DRUG:	ORAPRED ODT (prednisolone sodium phosphate Orally Disintegrating Tablets, 10 mg, 15 mg and 30 mg tablets)
NDA:	21-959
SPONSOR:	BioMarin Pharmaceutical Inc.
INDICATION:	multiple indications

BioMarin Pharmaceutical, Inc. submitted their application for this new dosage form of prednisolone on August 1, 2005. As per the reviews by the clinical, clinical pharmacology and biopharmaceutics, pharmacology/toxicology and CMC teams, the sponsor has fulfilled the requirements for a 505(b)(2) application, no new safety concerns have been demonstrated, and the product quality is acceptable.

Action: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
6/1/2006 11:23:01 AM
MEDICAL OFFICER

Jani, Parinda

From: Jani, Parinda
Sent: Thursday, May 25, 2006 9:25 AM
To: 'Ruhi Ahmed'; 'awaterhouse@BMRN.com'
Subject: FW: NDA 21-959/ORAPRED

Hi Ruhi and Amy:

Couple of comments regarding the packaging labels.

Let me know if you have any questions.

Thanks

Parinda

DMETS has reviewed the submitted label and labeling changes from the 5/12/06 BL submission in the EDR for NDA# 21-959, and has identified some additional areas for improvement:

1. Blister Container Label

   Since each blister contains only one tablet, revise the text to read "Prednisolone sodium phosphate orally disintegrating tablet".

2. Carton Labeling

   In the current presentation, the height of the established name is ½ of the proprietary name; however, the bolded font of the proprietary names gives the appearance that the proprietary name is significantly larger than the established name. Additionally, the strength is not easily identifiable as currently presented. Increase the size of the established name and strength.

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/s/

Parinda Jani
5/25/2006 10:06:12 AM
CSO

Jani, Parinda

From: Jani, Parinda
Sent: Wednesday, May 24, 2006 7:43 PM
To: 'Amy Waterhouse'
Cc: 'Ruhi Ahmed'
Subject: RE: NDA 21-959, Orapred ODT, CMC Information Request Amendment

Hi Ruhi and Amy:

Please clarify the following:

"Clarify that the barcode contained on the blister labels has the NDC number encoded in it. Note that this is a requirement of the barcode rule. Also, state whether the barcode contains information on the lot number and expiration dating period."

Thanks

Parinda

From: Amy Waterhouse [mailto:awaterhouse@BMRN.com]
Sent: Tuesday, May 23, 2006 4:45 PM
To: Jani, Parinda
Cc: Ruhi Ahmed
Subject: NDA 21-959, Orapred ODT, CMC Information Request Amendment

Dear Ms. Jani,

Attached is a CMC amendment to NDA 21-959 in response to the request from the Agency in an email dated May 22, 2006.

We will send the hard copy version today by Federal Express for receipt tomorrow.

Please contact me or Ruhi Ahmed at 415-250-2676 if you have any questions regarding this amendment.

Kind regards,

Amy Waterhouse
Vice President, Regulatory and Government Affairs
BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

office 415-506-6708 fax 415-506-6306
awaterhouse@bmrn.com

www.bmrn.com

<<CMC_Letter__3.pdf>>

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/s/

Parinda Jani
5/25/2006 10:04:52 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 24, 2006

TO: Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products (DAARP)

FROM: John A. Kadavil, Ph.D.
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 21-959, Orapred ODT™, Sponsored by Medicis Pharmaceutical Corporation

At the request of DAARP, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Study Number: **OPD-001-01**

Study Title: "Comparative, Randomized, Single-Dose 3-way Crossover Relative Bioavailability Study of Orapred® Orally Disintegrating Tablet (Prednisolone Sodium Phosphate) 40.3 mg (Equivalent to 30 mg Prednisolone Base) vs Celltech Pediapred® (Prednisolone Sodium Phosphate) Oral solution 6.7 mg/5 mL (Equivalent to 5 mg Prednisolone Base/5 mL) and Orapred® (Prednisolone Sodium Phosphate) Oral Solution 20.2 mg/5 mL (Equivalent to 15 mg Prednisolone Base/5 mL) in Healthy Volunteers Under Fasting Conditions"

The clinical portion of the study was conducted at [redacted] from 3/15/05 - 3/29/05. The analytical portion of the study was conducted at [redacted] from 4/29/05 - 5/3/05.

Following the inspections at [redacted] (3/28/06 - 4/4/06), and [redacted] (3/13/06 - 3/16/06), no significant clinical or analytical issues were identified, and no Form FDA 483 was issued.

Conclusion:

DSI recommends that Study OPD-001-01 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

John A. Kadavil, Ph.D.

Final Classification:
NAI - [redacted]
NAI - [redacted] **(This NAI classification pertains only to Study OPD-001-01, analytical report date 7/12/05, under NDA 21-959)**

cc:
HFD-45/RF
DSI GLP-BE/Kadavil(2)/Himaya/CF
OCPB-DCPB2/Doddapaneni/Lee/NDA 21-959
OAP-DAIOP/Dean/NDA 21-959
HFR-CE3565/Marciante
HFR-SW3510/Breithaupt
Draft: JAK 4/24/06
Edit: MKY
DSI: 5673; O:\BE\EIRCOVER\21959med.ora.doc
FACTS: 717116 and 706814

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/s/

John Kadavil
5/15/2006 02:19:20 PM
PHARMACOLOGIST
Paper copy signed by Sriram Subramaniam and available upon request.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-959

DISCIPLINE REVIEW LETTER

BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

Attention: Ruhi Ahmed, Ph.D., RAC
Manager, Regulatory Affairs

Dear Dr. Ahmed:

Please refer to your July 28, 2005 new drug application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Orapred ODT (prednisolone sodium phosphate) Orally Disintegrating Tablets.

The Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety, has completed the review of your trade name and carton and container labels and have identified the following deficiencies. DMETS has attempted to focus on safety issues relating to possible medication errors, and has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. The strength of this product is based on the active moiety Prednisolone and not the salt Prednisolone Sodium Phosphate. In the current presentation, the established name includes the salt and the Prednisolone equivalent and both are presented on the label without clarification. We recommend revising the established name on the labels and labeling to one of the following examples:

2. The established name appears less than ½ the size of the proprietary name. Increase the prominence of the established name so that it is at least ½ the size of the proprietary name per the requirements of 21 CFR201.10(g)(2). Similarly, increase the font size of the product strength so that it is more prominent and legible in comparison to the proprietary and established names.

3. Revise the proprietary name Orapred to appear in a straight line. The font used makes the name look handwritten and difficult to read. [redacted] Revise accordingly.

4. The display of grapes, outline of grapes, and colored 'waves' interfere with the readability of the proprietary and established names, as well as the strength. Additionally, the graphics are more prominent than the proprietary and established names and strength. [redacted]

5. Ensure that the labels and labeling for Orapred ODT are distinct from Orapred and Orapred RT*** to decrease the potential for selection errors.

6. Add the statement "Do not break or use partial ODT tablets" to all labels and labeling. Additionally, if space permits, include the warning 'Do not remove the tablet from the blister until just prior to dosing'.

B. BLISTER LABEL

1. See GENERAL COMMENT A1, A2 and A6.

2. The blister label appears crowded. We recommend deleting the ' [redacted] statement to allow for more room. See comment A1.

3. Ensure the established name is ½ the size of the proprietary name and the prominence of the strengths is commensurate with that of the established name.

4. Include directions for removal of the tablet from the blister pack, (e.g. peel, etc.) to prevent patients from pushing the tablet through the blister.

5. The layout and colors used to designate the 10 mg, 15 mg, and 30 mg are identical. [redacted]

C. CARTON LABELING

1. See GENERAL COMMENTS.

2. The established name and strength are separated by a purple line. Delete the line as there should be no intervening matter between the drug name and strength.

3. Revise net quantity to read ' [redacted] which accurately reflects the composition of the cards.

D. INSERT LABELING

1. Revise the statement in the **HOW SUPPLIED** section from '' [redacted] to '8 cards containing 6 tablets'.

2. The **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections contain the statement 'Do not break or use partial ODT tablets'. We recommend that this information be bolded to provide greater prominence in order to reflect the importance of this information.

If you have any questions, call me at (301) 796-1232.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
5/3/2006 10:47:18 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-959

INFORMATION REQUEST LETTER

Medicis Pediatrics, Inc.
8125 N. Hayden Road
Scottsdale, AZ 85258

Attention: R. Todd Plott, MD
VP, Clinical Research & Regulatory Affairs

Dear Dr. Plott:

Please refer to your July 25, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orapred ODT™ (prednisolone sodium phosphate) orally disintegrating tablets, 10 mg, 15 mg and 30 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide reference to appropriate CFR sections (indirect food additives) for the ——— for the storage of the ——— PSP.

2. Include a test for microbial limits in the drug product specification for shelf life; or provide appropriate justification to indicate that microbial growth is not an issue with the formulation.

3. Provide updated stability data, with statistical analysis (SAS transport files) if appropriate, to justify the proposed expiration dating period.

4. In the proposed specification for ——— PSP, the test for the particle size included acceptance criteria for ——— and ——— But in Module 3, vol.1, page 141, it was stated that screening was done with only ——mesh sieve, not ——mesh sieve. Clarify.

5. Provide a statement that the blend uniformity testing, and in-process content uniformity testing would be carried out on the first three commercial batches in accordance with the provisions described in the draft guidance on powder blends (Guidance for Industry: Powder Blends and Finished Dosage Units - Stratified In-Process Dosage Unit Sampling and Assessment). Based on the results, blend uniformity testing may be dropped, but in-process content uniformity testing would be continued on reduced sample size.

6. Please explain how the seal integrity test is equivalent or superior to USP<671> moisture permeation test for blisters. Alternatively, if you have data on USP moisture permeation test for the proposed blister, please provide it.

7. Please revise the dissolution acceptance criteria to —% in 30 minutes from —% in 30 minutes.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-796-1202.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jane Dean
3/15/2006 01:38:09 PM
Signed for Parinda Jani

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 21-959 SUPP TYPE & # _____ Division 170 UFID # 3006144

Applicant Name: Medicis Drug Name: Orapred ODT

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?
   ☑ Yes ☐ No

2. Firm in Arrears?
   ☐ Yes ☑ No

3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" http://www.fda.gov/cder/guidance n/a
   ☐ Yes ☐ No (explain in comments)

4. Administrative Split? (list all NDA#s and Divisions)

NDA #/Doc Type	Div.	Fee? (Y/N)
n/a		

5. Type 6?
   ☐ Yes ☑ No

   Type 6 to which other application?

   NDA #_____ Supp Type &#_____

6. Clinical Data Required for Approval? (Check one)
   ☐ Yes*

   ☐ Yes, by reference to another application

   NDA #_____ Supp Type & #_____

   ☑ No

   * Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)" http://www.fda.gov/cder/guidance
   ☑ Yes ☐ No ☐ To be determined

8. Subpart H (Accelerated Approval/Restricted Distribution)?
   ☐ Yes ☑ No ☐ To be determined

9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)

   List of exclusions:

   2 – No fee - administrative split
   4 – No fee - 505b2
   7 – Supplement fee - administrative split
   9 – No fee Subpart H supplement– confirmatory study
   11 – No fee Orphan Exception
   13 – No fee State/Federal exemption from fees

10. Waiver Granted?
    ☐ Yes (letter enclosed) ☑ No

    Select Waiver Type below: Letter Date: _____

    ☐ Small Business ☐ Barrier-to-Innovation
    ☐ Public Health ☐ Other (explain)

11. If required, was the appropriate fee paid?
    ☑ Yes ☐ No

12. Application Review Priority
    ☐ Priority ☑ Standard ☐ To be determined

13. Fast Track/Rolling Review Presubmission?
    ☐ Yes ☑ No

Comments

Jane Dixon 12-24-06
PM Signature/Date

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

CC: original archival file
HFD-007

Processor Name & Date _____

QC Name & Date _____

(8/18/03)

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; WO 22, STOP: 4447)

DATE RECEIVED: February 13, 2006 **DATE OF DOCUMENT:** July 28, 2005	**DESIRED COMPLETION DATE:** May 1, 2006 **PDUFA DATE**: May 28, 2006	**ODS CONSULT #:** 06-0047

TO: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170

THROUGH: Linda Kim-Jung, PharmD., Team Leader
Denise Toyer, PharmD., Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Orapred ODT**
(Prednisolone Sodium Phosphate Orally Disintegrating Tablets)
10 mg, 15 mg, and 30 mg (base)

NDA#: **21-959**

DA SPONSOR: **Medicis Pharmaceuticals**

SAFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Orapred ODT. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Orapred ODT, acceptable from a promotional perspective.

DMETS would appreciate feed back of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-959 Supplement # Efficacy Supplement Type SE- n/a

Trade Name: Orapred ODT
Established Name: prednisolone sodium phosphate orally disintegrating tablets
Strengths: 10 mg, 15 mg and 30 mg prednisolone base

Applicant: Medicis Pediatrics, a wholly owned subsidiary of Medicis Pharmaceutical Corp.
Agent for Applicant: BioMarin Pharmaceuticals, Inc.

Date of Application: July 28, 2005
Date of Receipt: August 1, 2005
Date clock started after UN: n/a
Date of Filing Meeting: September 23, 2005
Filing Date: September 30, 2005
Action Goal Date (optional): May 15, 2006 User Fee Goal Date: June 1, 2006

Indication(s) requested: Endocrine, dermatologic, rheumatic, hematologic disorders, allergic states, ophthalmic, respiratory, neoplastic, gastrointestinal diseases, edematous states, nervous system disorders and miscellaneous disorders

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☒ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) n/a

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication*

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☒ YES ☐ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: n/a

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) April 11, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☒
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 23, 2005

BACKGROUND: Medicis Pharmaceutical corp.has submitted the NDA for Orapred ODT™, 10 mg, 15 mg and 30 mg prednisolone Orally Disintegrating Tablets (equivalent to 13.44 mg, 20.16 mg and 40.32 mg of prednisolone sodium phosphate). The submission is relying on the FDA's previous findings of safety and effectiveness of the reference listed drug Pediapred® Oral Solution, 6.7 mg / 5mL (prednisolone base 5 mg/ 5mL), via cross reference to NDA 19-157 (Pediapred®). The sponsor is also submitting the results of two relative bioavailability studies that compared the bioequivalency of Orapred ODT™ with the reference listed drug Pediapred® and the relative bioavailability of Orapred ODT™ with and without water, respectively.

ATTENDEES: Parinda Jani, Constantine Markos, Julie Castle, Rao Puttagunta, Lawrence Leshin, Srikanth Nallani, Yongman Kim, Sharon Hertz, Joel Schiffenbauer, John L. Smith, Josie Yang, Thomas Permutt, Suresh Doddapaneni, Bob Rappaport

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Castle
Secondary Medical:	
Statistical:	Yongman Kim
Pharmacology:	Leshin
Statistical Pharmacology:	
Chemistry:	Puttagunta
Environmental Assessment (if needed):	
Biopharmaceutical:	David Lee
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Markos, Rana, Dean
Other Consults:	OGD, DDMAC, DMETS

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS	N/A	☒	FILE	☐	REFUSE TO FILE	☐
BIOPHARMACEUTICS			FILE	☒	REFUSE TO FILE	☐
• Biopharm. inspection needed?					YES ☒	NO ☐
PHARMACOLOGY	N/A	☐	FILE	☒	REFUSE TO FILE	☐
• GLP inspection needed?					YES ☐	NO ☒
CHEMISTRY			FILE	☒	REFUSE TO FILE	☐
• Establishment(s) ready for inspection?					YES ☒	NO ☐
• Microbiology					YES ☐	NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Jane A. Dean, RN, MSN
Regulatory Project Manager, HFD-170

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): **NDA 19-157 (Pediapred™)**

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☒ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☒

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). *This application provides for a change in formulation from a solution to an orally disintegrating tablet*

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☒ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☒

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☒ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☒ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☒ NO ☐

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/

Jane Dean
2/23/2006 03:34:17 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Carolanne Currier HFD- 45			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Pratibha Rana Division of Anethesia, Analgesia, and Rheumatology Products, HFD-170	
DATE 01-20-06	IND NO.	NDA NO. 21-959	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT July 25, 2005
NAME OF DRUG Orapred ODT	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE May 1, 2006 (PDUFA Due date is June 1)

NAME OF FIRM: [redacted]

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

DSI-BE Inspection is requested for the following:

Study #: OPD-001-01
Title: Comparative, Randomized, Single-Dose 3-way Crossover Relative Bioavailability Study of Orapred Orally Disintegrating tablet (Prednisolone Sodium Phosphate) 40.3 mg (Equivalent to 30mg Prednisolone Base) vs Celltech Pedipred (prednisolone Sodium Phsophate) Oral Solution 6.7 mg/5 mL (Equivalent to 5mg Prednisolone Base/5 mL) and Orapred (prednisolone Sodium Phosphate) Oral Solution 20.2 mg/5mL (equivalent to 15 mg Prednisolone Base/5 mL) in Healthy Volunteers under Fasting Conditions
Clinical Investigator: [redacted]

Analytical Investigator: [redacted]

[redacted] This is a new NDA

\ copy of the BE report will be send to you. Please let me know if you have any question.

Thank You,
Pratibha Rana
CSO
301-796-1277

SIGNATURE OF REQUESTOR Pratibha Rana	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☒ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Pratibha Rana
1/20/2006 01:50:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-959

Medicis Pediatrics, Inc.
Attention: Ruhi Ahmed, Ph.D.
Manager, Regulatory Affairs
BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

Dear Dr. Ahmed:

Please refer to your July 25, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orapred ODT (Prednisolone Sodium Phosphate Orally Disintegrating Tablets, 10 mg, 15 mg, and 30 mg Prednisolone base.)

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 30, 2005 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Tables that are referenced are not labeled with titles, for example, Table 2.7.1.1, or Table 2.7.1.2. Please list all of the tables with titles, include table number, and page numbers.

2. Confirm that there were no discontinuations, as none were mentioned in the NDA.

3. If collected, submit data related to the time it took for the tablets to disintegrate/dissolve on the tongue of each subject participating in Studies OPD-001-01 and/or OPD-002-01.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Constantine J. Markos, Pharm.D., Regulatory Health Project Manager, at (301) 796-1252.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
10/14/2005 06:17:38 PM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-959	Brand Name	Orapred ODT™
OCPB Division (I, II, III)	DPE II	Generic Name	Prednisolone Sodium
Medical Division	Division of Analgesics Anesthetics and Rheumatology Products	Drug Class	Glucocorticoid Anti-inflamatory agent
OCPB Reviewer	Srikanth C. Nallani, Ph.D.	Indication(s)	
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Orally Disintegrating Tablets
		Dosing Regimen	60 mg per day
Date of Submission	7/28/2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	3/28/2005	Sponsor	Medicis Pediatrics, Inc.,
PDUFA Due Date	5/28/2005	Priority Classification	Standard
Division Due Date	4/28/2005		

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	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Reports were submitted as part of the PK studies
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:	**X**	1		**Relative bioavailability of Orapred ODT vs Orapred oral solution (study OPD-001-01)**
alternate formulation as reference:	**X**	1		**Relative bioavailability of Orapred ODT with and without water consumption (study OPD-002-01)**
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		**Single dose 3-way cross over Orapred ODT, Pediapred (RLD), Orapred oral solution**
replicate design; single / multi dose:				
Food-drug interaction studies:				Matter resolved at a Pre-NDA meeting
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				**see QBR questions**
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		More than one aspect is covered by single study.

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**Will be sent**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. (1) If collected, submit data related to the time it took for the tablets to disintegrate/dissolve on the tongue of each subject participating in studies OPD-001-01 and/or OPD-002-01
QBR questions (key issues to be considered)	Is the test product (Orapred) bioequivalent with the reference listed drug product? Is there any difference in PK of prednisolone when Orapred is consumed with or without water? Is the food effect appropriately addressed? Are lower strengths eligible for a biowaiver? Is the analytical method adequately validated? Is the dissolution method and specifications appropriate for this product?	

Other comments or information not included above	The pivotal BE study OPD-001-01 needs to be inspected by DSI and a DSI consult will be initiated
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

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/s/

Srikanth Nallani
10/3/2005 11:29:58 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
10/3/2005 11:33:44 AM
BIOPHARMACEUTICS

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: 21-959 **Applicant: Orapred ODT** **Stamp Date: 8-1-05**
Drug Name: Orapred ODT

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? Yes [x] No [ ]

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?			see note below
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review begin?			
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?			
4	Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?			
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?			
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?			
7	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?			
8	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?			
9	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			
10	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?			
11	From a pharmacology perspective, is this NDA fileable?			

Note:

The pharmtox section, Module 4, Nonclinical Studies, consisted of section 4.2 Study Reports and was marked by the sponsor as "Not Applicable."
This is a 505(b)(2) application.

Reviewing Pharmacologist: _____

Date:

Team Leader: _____

Date:

cc:
Original NDA
HFD-170/Division File
HFD-170/Pharm-Tox/Leshin
HFD-170/Pharm-ToxTL/Yang
HFD-170/MO/Castle
HFD-170/PM/Markos

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/s/

Lawrence Leshin
9/26/2005 04:38:33 PM
PHARMACOLOGIST

Josie Yang
9/26/2005 05:55:15 PM
PHARMACOLOGIST

NDA FILEABILITY CHECKLIST (CMC)

NDA Number: 21-959 **Applicant:** Medicis Pediatrics, Inc. **Stamp Date:** 8/01/05
Drug Name: Orapred ODT™ (Prednisolone Sodium Phosphate) Orally Disintegrating Tablets, 10, 15 and 30 mg

IS THE CMC SECTION OF THE APPLICATION FILABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	✓		
2	Is the section indexed and paginated adequately?	✓		
3	On its face, is the section legible?	✓		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	✓		Module 3, volume 1, pages 8 and 191
5	Is a statement provided that all facilities are ready for GMP inspection?	✓		Module 1, volume 1, page 17
6	Has an environmental assessment report or categorical exclusion been provided?	✓		Module 1, volume 1, page 250
7	Does the section contain controls for the drug substance?	✓		Module 2, volume 1, page 12
8	Does the section contain controls for the drug product?	✓		Module 2, volume 1, pages 52, 53, and 54
9	Has stability data and analysis been provided to support the requested expiration date?	✓		Module 3, volume 3a, page 276 6 months of stability data at 25°C/60%RH and 40°C/65%RH on two pilot scale batches each of 10, 15 and 30 mg tablets was provided. Stability data for 18 months at 25°C/60%RH and 6 months at 40°C/65%RH on one lab scale batch each of 10 mg and 30 mg of drug product was provided. The tablets were packaged in six count blisters. Proposed expiration dating period: 24 months
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			N/A
11	Have draft container labels been provided?	✓		Module 1, volume 1, page 255
12	Has the draft package insert been provided?	✓		Module 1, volume 1, page 279
13	Has an investigational formulations section been provided?	✓		Pharmaceutical development (3.2.P.2)
14	Is there a Methods Validation package?	✓		
15	Is a separate microbiological section included?		✓	N/A

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Reviewing Chemist: Rao Puttagunta, Ph.D. Date: 9/22/05

NDA Number: 21-959 **Applicant**: Medicis Pediatrics, Inc. **Drug Name**: Orapred ODT™ (Prednisolone Sodium Phosphate) Orally Disintegrating Tablets, 10, 15 and 30 mg

Have all DMF References been Identified? YES

DMF Number	Type	Holder	Description	LOA
[redacted]	II	[redacted]	Prednisolone Sodium Phosphate	10/12/04
[redacted]	IV	[redacted]	[redacted]	5/18/05
[redacted]	IV	[redacted]	[redacted]	4/05/05
[redacted]	III	[redacted]	[redacted]	7/05/05
				5/25/05
[redacted]	III	[redacted]	[redacted]	7/14/05

APPEARS THIS WAY

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/s/

Rao Puttagunta
9/22/2005 11:11:49 AM
CHEMIST

John Smith
9/22/2005 11:17:50 AM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-959

Medicis Pediatrics, Inc.
Attention: Ruhi Ahmed, Ph.D.
Manager, Regulatory Affairs
BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

Dear Dr. Ahmed:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Orapred ODT (Prednisolone Sodium Phosphate Orally Disintegrating Tablets, 10 mg, 15 mg, and 30 mg Prednisolone base.)

Review Priority Classification: Standard (S)

Date of Application: July 25, 2005

Date of Receipt: August 1, 2005

Our Reference Number: NDA 21-959

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 30, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 1, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Since oral prednisolone solution is available for titrating doses in pediatric populations we are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic, mixed electronic and paper, or paper only submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Constantine J. Markos, Pharm.D., Regulatory Health Project Manager, at (301) 827-2496.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
9/13/2005 12:26:46 PM

Original NDA
Orapred ODT™
Medicis Pharmaceutical Corporation

ENVIRONMENTAL IMPACT ANALYSIS STATEMENT

Orapred ODT™

10 mg, 15 mg and 30 mg Prednisolone* Orally Disintegrating Tablets
(*Equivalent to 13.44 mg, 20.16 mg, and 40.32 mg of Prednisolone Sodium Phosphate)

In accordance with 21 CFR §25.31(a), Medicis Pharmaceutical Corporation and BioMarin Pharmaceutical Inc., hereby claim a Categorical Exclusion from the requirement of filing an Environmental Impact Analysis statement, since Orapred ODT Tablets will not increase the use of the active moiety, Prednisolone Sodium Phosphate, USP.

With regard to the production of Orapred ODT Tablets, 10 mg, 15 mg and 30 mg Prednisolone, Medicis Pharmaceutical Corporation and BioMarin Pharmaceutical Inc., also certify that we are in compliance with all appropriate Federal, State and Local environmental regulations and laws.

Additionally, Medicis Pharmaceutical Corporation and BioMarin Pharmaceutical Inc., state that to the applicant's knowledge, no extraordinary circumstances exist and we are not aware of any information that the substance may be toxic to organisms in the environment.

R. Todd Plott, M.D.
Vice President,
Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corporation

7/25/05
Date

Ruhi Ahmed, Ph.D.
Manager, Regulatory Affairs
BioMarin Pharmaceutical Inc.
Regulatory Agent

July 18, 2005
Date

MEMORANDUM OF TELECON

DATE: July 11, 2005

APPLICATION NUMBER: PIND 70,495 Orapred ODT

BETWEEN:

Name: Ruhi Ahmed, PhD- Regulatory Affairs
Phone: (415) 506-6735
Representing: BioMarin Pharmaceutical, Inc.

AND

Name: Sharon H. Hertz, MD
Division of Anesthesia, Analgesia, and Rheumatology Products

SUBJECT: ISS/ISE requirements and clarification of proposed label

BioMarin met with the Division April 11, 2005 for a Pre-NDA meeting. They propose a label combining their 10 mg orally disintegrating tablet (ODT) with Orapred Solution used for doses less than 10 mg. BioMarin is the regulatory authority for Orapred Solution (ANDA 75-117).

The following points were noted during the teleconference:

1. The sponsor clarified that although they own Orapred Solution, they chose Pediapred Solution (NDA 19-157) as the reference listed product (RLD) because this application contained the data supporting approval upon which the Orapred Solution ANDA was based.
2. The integrated summary of efficacy (ISE) is a necessary component of the NDA. In the case of a 505(b)(2) application that will not contain clinical efficacy studies, the ISE would consist of the data describing why it is appropriate to rely on prior findings of efficacy for the RLD, such as bioequivalence.
3. The integrated summary of safety (ISS) should include results from a literature review and safety reports of the active moiety, prednisolone sodium phosphate. As a similar review was performed for the Orapred Solution generic application, the information from that application along with the any new information in the two years subsequent to approval would be adequate. The sponsor will also provide information from safety reports for Orapred Solution. The emphasis will be on safety concerns that differ from the existing package insert for the reference listed product. Summary tables will be provided.
4. The division noted [redacted] and will provide further feedback as information is received from the Office of Generic Drugs.
5. The sponsor confirmed that they are not pursuing a dose less than 10 mg per ODT tablet.
6. The limited dosing flexibility presented by the lowest proposed formulation of 10 mg would be reflected in the labeling, including effects on pediatric dosing indications. The

sponsor acknowledged this potential impact on labeling.

7. The Division will work with the sponsor to develop an appropriate label considering the above discussion.

Sharon, H. Hertz, MD
Deputy Director

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/s/

Nancy Clark
7/13/05 09:46:08 AM
CSO

Sharon Hertz
7/15/05 11:21:21 AM
MEDICAL OFFICER

Bob - not sure what to do with this
for sign off. this was a recent telecon
with sponsor.

Bob Rappaport
7/15/05 05:21:54 PM
MEDICAL OFFICER

.: Clark, Nancy
Sent: Monday, June 20, 2005 4:09 PM
To: 'Ruhi Ahmed'
Subject: food effect study PIND 70495

Ruhi, I have provided the comments from Clinical Pharmacology regarding the food effects study.
Thank you, Nancy

Comments: Based on the assumption that bioequivalence (BE) between Orapred ODT and the reference listed drug (RLD) can be established, a food-effect study on Orapred ODT will not be necessary. However, if BE cannot be established, the sponsor needs to conduct food effect study on Orapred ODT.

Nancy Clark, PharmD.
Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Rheumatology Products, HFD-550
Center for Drug Evaluation and Research
9201 Corporate Boulevard, Rm N345
Rockville, MD 20850
phone: 301-827-2516
mile: 301-827-2531

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/s/

Nancy Clark
6/21/05 10:25:45 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 70,495

BioMarin Pharmaceutical Inc.
Attn: Cordelia K. Leonard
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Leonard:

Please refer to your Pre-Investigational New Drug (PIND 70,495) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Orapred ODT™ (prednisolone sodium phosphate) Orally Disintegrating Tablets 10 mg, 15 mg, and 30 mg equivalent to prednisolone base.

We also refer to the meeting between representatives of your firm and the FDA on April 11, 2005. The purpose of the meeting was to obtain FDA input on the NDA submission strategy for Orapred ODT™.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nancy Clark, PharmD, Regulatory Project Manager, at (301) 827-2516.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, Ph.D, M.D.
Acting Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmologic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

Sponsor Meeting Minutes

MEETING DATE: April 11, 2005

TIME: 2:45-3:40 p.m.

LOCATION: S300, 9201 Corporate Boulevard, Rockville, MD

APPLICATION (DRUG): PIND 70,495 (Orapred ODT)

SPONSOR: BioMarin Pharmaceutical Inc.

TYPE OF MEETING: PreNDA, face to face

MEETING CHAIR: Brian Harvey, MD, PhD

MEETING RECORDER: Nancy Clark, PharmD

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
Brian E. Harvey, MD, PhD	Acting Director	ODEV/DAAODP, HFD-550
Joel Schiffenbauer, MD	Assigned Clinical Team Leader	ODEV/DAAODP, HFD-550
John Smith, PhD	Chemistry Team Leader	ONDC
Tapash Ghosh, PhD	Clinical Pharmacology & Biopharmaceutics Reviewer	Division of Pharmaceutical Evaluation III (DPEIII)
Nancy Clark, PharmD	Regulatory Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
Robert Baffi, Ph.D.	Senior Vice President, Technical Operations	BioMarin (Agent)
Celeste Decker, M.D.	Manager, Medical Affairs	BioMarin (Agent)
Cori Leonard	Associate Director, Regulatory Affairs	BioMarin (Agent)
Frank Sorgi, Ph.D	Associate Director, Program Management	BioMarin (Agent)
Amy Waterhouse	Senior Director, Regulatory Affairs	BioMarin (Agent)
Stewart Swiedler, MD, PhD	Senior Vice President, Clinical Affairs	BioMarin (Agent)
Jim Klancke	Senior Director, Analytical Development	CIMA (Manufacturer)
Derek Moe, Ph.D	Senior Director, Product Development	CIMA (Manufacturer)
Philip Simonson, Ph.D	Senior Director, Regulatory Affairs	CIMA (Manufacturer)
	Pharmacokinetics and Pharmacology	Consultant

PURPOSE OF MEETING AND GENERAL BACKGROUND

The primary purpose of the meeting is to obtain confirmation of the acceptability of their 505(b)(2) registration strategy through understanding of the key elements of the Orapred ODT program, i.e., current chemistry, manufacturing and controls information and bioequivalence study design.

OBJECTIVES

BioMarin would like to obtain input from the Division concerning the overall regulatory submission strategy for Orapred ODT, specifically:

1. Confirmation that the proposed orally disintegrating tablet formulation of prednisolone sodium phosphate can be reviewed as a 505(b)(2) application based on FDA's previous findings of safety and effectiveness of Pediapred.
2. The adequacy of the chemistry, manufacturing and controls information.
3. The adequacy of dissolution and impurity profiles, together with the proposed bioequivalence studies, to support the nonclinical and clinical portions of the 505(b)(2).

Meeting Discussion:

BioMarin disclosed that Orapred ODT will target pediatric and geriatric patient populations and that they plan on filing an NDA 505(b)(2) in 2006.

Regulatory Questions

1. Does the Division agree that Orapred ODT can be submitted as a 505(b)(2) application?

   FDA Response:

   Yes, your Orapred ODT (prednisolone sodium phosphate) application can be submitted as a 505(b)(2) application.

Meeting Discussion:
BioMarin acknowledged FDA response.

2. BioMarin is proposing to submit a paper NDA with electronic SAS files for the bioequivalence study Case Report Tabulations. Does the Division have any comments concerning this approach?

   FDA Response: Yes, that is acceptable.

Meeting Discussion:
BioMarin acknowledged FDA response.

3. For the Environmental Assessment requirement, does the Division agree that Orapred ODT qualifies for a categorical exclusion?

   FDA Response:

   We agree that Orapred ODT qualifies for a categorical exclusion from the requirement for an environmental assessment (EA). Our regulation at 21 CFR 25.31(a) provides that approval of an NDA will ordinarily be excluded from EA requirements on this ground (assuming the agency agrees it applies), unless any "extraordinary circumstances indicate that the proposed action [i.e., approval of the NDA] may significantly affect the quality of the human environment" (21 CFR 25.21). Your request for a categorical exclusion appears acceptable. Note that, in your background package, BioMarin cites 21 CFR 25.31(b) in support of your request for EA exclusion, but the reason you give actually corresponds to 21 CFR 25.31(a)].

Meeting Discussion:
BioMarin acknowledged error in background package and accepts FDA response.

Clinical Questions

4. BioMarin intends to rely on the FDA's previous findings of the safety and effectiveness of Pediapred via cross–reference to NDA 19–157. Does the Division agree that this approach, in conjunction with the bioequivalence study, is acceptable and that no additional clinical studies are necessary?

   FDA Response:

   Yes.

   - In terms of the two proposed bioequivalency (BE) studies (OPD-001-01 and OPD-002-01), you may choose to conduct study OPD-001-01 with ODT formulation given without water. If ODT without water and RLD with water are found to be BE, then it may not be necessary to study the effect of water (OPD-002-01). A labeling claim that ODT can be taken with or without water can be granted. In light of this, we recommend that you modify protocol OPD-001-01 and plan to proceed for OPD-002-01 sequentially, in case the need arises.
   - You will need to study the effect of food on the pharmacokinetics of Orapred ODT.

Meeting Discussion:

BioMarin acknowledged FDA response in the first bulleted point. Regarding the food effects study, BioMarin felt it unnecessary to conduct a food effect study for three reasons. First, the *in vitro* dissolution data suggests that Orapred ODT behaves like a liquid. Second, published literature indicates a lack of food effect for prednisolone. Third, the reference listed drugs (RLDs), Pediapred and Orapred Solution, do not mention food effects in their label.

FDA Clinical Pharmacology mentioned that the Agency's view on conducting a food effect study for an ODT is "If food has not affected the BA of the active drug in the conventional oral dosage form (COD), a similar lack of food effect may be expected with an ODT. If BE has been already been established between the COD and the ODT, then a food effect study would not be necessary." BioMarin agreed to submit a summary of the published literature to the PIND file for review prior to the NDA application. FDA will contact BioMarin after reviewing the literature about whether a food effect study is still necessary for Orapred ODT and if the study needs to be initiated prior to filing the NDA.

5. The current Orapred and Pediapred package inserts contain dosing data for the pediatric population. Does the Division agree that the information contained in these package inserts under the heading "Pediatric Use" is adequate to satisfy the need for pediatric assessment of Orapred ODT (i.e., a waiver for additional pediatric studies will be granted)?

   FDA Response:

   The current label for Pediapred states that the dose range is 5-60 mg daily. You propose 10, 15, and 30 mg dosage forms for the ODT. Thus it will not be feasible to taper the doses below 10 mg using the ODT, nor to administer regular doses of less than 10 mg, which may be particularly pertinent for pediatric patients. Provide a rationale for the proposed dosage forms and provide a means for how doses less than 10 mg will be managed.

Meeting Discussion:

BioMarin seeks to obtain the same numerous indications as the RLDs. In order to write dosing instructions in the label, tapering must be included. Since 10 mg is the smallest strength of the Orapred ODT tablet, FDA suggested a 2.5 mg tablet to provide dosing flexibility. FDA and BioMarin agreed that BioMarin would submit a concrete proposal to address dosing lower than 10 mg. FDA will determine how best to handle dosing of Orapred for patients needing less than 10 mg such as recommending a change to the solution.

FDA relayed that the Division of Pediatric Drug Development did not recommend conducting a pediatric study.

Nonclinical Questions

6. BioMarin intends to rely on the FDA's previous findings of the safety and effectiveness of Pediapred via cross–reference to NDA 19–157. Does the Division agree that this approach is acceptable and that no additional studies are necessary?

FDA Response:

No additional non-clinical study is necessary. Reference to NDA 19-157 is acceptable.

Meeting Discussion:
BioMarin acknowledged FDA response.

Chemistry and Manufacturing Questions

7. BioMarin is proposing to submit stability data from a total of eight stability lots to support the dosage strengths of 10 mg, 15 mg, and 30 mg. The lower and upper dosage strengths, 10 mg and 30 mg, respectively, will be supported by two lots each manufactured at a —% scale and one lot each at pilot scale (three lots total per 10 mg and 30 mg strength). The bracketed 15 mg dosage strength will be supported by two lots manufactured at a —% scale. Each dosage strength is manufactured from a ———. Does the Division agree with this approach?

FDA Response:

Yes, submission of data on the eight batches will be sufficient, provided that no issues concerning drug product stability are found during the stability studies, and provided that the differences in formulation between the pilot batches and proposed commercial batches are not significant.

Meeting Discussion:

During the scaling up of production, the target formulation was changed to accommodate a change in tablet size. BioMarin presented two slides comparing the formulations and stated that the stability data and degradation rates of the pilot batches and [redacted] scale batch were the same despite having different formulations. BioMarin suggested that, since the first manufacturing step is to put a [redacted]

BioMarin will send copies of the formulation and stability information for review. FDA will determine if the stability data from the pilot batches can be considered representative .

8. The impurity profiles observed for Orapred ODT, Orapred, and Pediapred are similar, and no new impurities have been observed in the proposed formulation. Does the Division agree that the impurities present in Orapred ODT are qualified, and that the limits in the ODT formulation can be justified on the basis of process capability and long term and accelerated stability data?

FDA Response:

Because of the nature of the impurities, we agree that there is no need for additional qualification data and that the acceptance criteria can be set based on process capability and long term and accelerated stability data.

Meeting Discussion:
BioMarin acknowledged FDA response.

9. Does the Division agree that the proposed tests in the drug product specifications are suitable for the control of this drug product?

FDA Response:

In general we agree that the proposed tests appear to be suitable for the control of the drug product. However:

(1) The description of the identity test and acceptance criterion were somewhat vague ("HPLC," "positive"), which raises the question of whether the test for identity will comply with the recommendations of ICH guidance Q6A (Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances), which indicates that identification solely on the basis of chromatographic retention time is not considered sufficient.

(2) The absence of microbial limits testing should be justified in the NDA. Since data collected during the pre-NDA period can strengthen the argument that such testing is not needed for the commercial drug, you may want to consider adding microbial limits testing to the pre-approval drug product specification.

Meeting Discussion:

BioMarin acknowledges FDA response and will address this in the NDA application.

10. BioMarin is proposing to submit up to 18 months of real–time and up to 6 months of accelerated stability data to support the requested 24 month expiration date at approval. Does the Division agree that this approach is acceptable?

FDA Response:

The amount of stability data that you propose to submit in the application (i.e., 18 months for the pilot batches but only 6 months for others) is sufficient for filing. Extrapolation of expiry beyond the time period covered by long-term data can be proposed, but the decision whether a 24-month expiry should be approved will be made during the review of the NDA, based on the submitted information. We recommend that you update the stability data in the NDA toward the end of the review cycle (e.g., 2-3 months before the PDUFA goal date) with all the stability data available at that time.

Meeting Discussion:
BioMarin acknowledged FDA response.

Additional CMC comments:

The Center's current thinking on orally disintegrating tablets is that they should disintegrate rapidly in the oral cavity during actual patient use and within 30 seconds during in vitro testing (using USP disintegration test procedure). Since the acceptance criterion currently listed for the drug product's in vitro disintegration test is NMT ___ seconds, and the test data indicate that some samples took more than 30 seconds to disintegrate, it appears that this product's performance may not meet the Center's expectations. Please provide samples of the drug product (e.g., lots 740553, 740556, 740557, and LB2066-05) at your earliest convenience for our analysis.

On page 12 of the pre-meeting package it is stated that the prednisolone sodium phosphate will meet USP requirements. This will not be considered sufficient. The drug substance specification should also include limits on impurities.

The proposed formulation provides for _____ This should be described in precise terms. (In other words, it should be clear how the _____ will be adjusted based on the potency, and how and when the potency will be determined.)

In stability study 740557.40, the assay was 97.6% at time zero, 102.9% at

1 month, and 97.3% at 3 months. Was an investigation made to determine the cause of the apparent 5% increase in assay value at the 1-month time station, and if so, to what was it attributed? (E.g., poor assay precision, evidence of batch non-uniformity?) Was any corrective action taken?

Meeting Discussion:
FDA explained that the limit of 30 seconds for *in vitro* disintegration time for ODT tablets is the current thinking of the Office of New Drug Chemistry. A guidance on ODTs that will address this issue is in development, but currently it is only an internal draft that has not yet been released for public comment. The USP disintegration test is currently the only one being discussed by FDA as a standard for in vitro testing. FDA allowed that adhering to the 30-second limit for disintegration time would probably not be needed if the product disintegrated rapidly enough in the experience of patients. FDA requested samples prior to submitting the NDA. The division project manager is the contact for this.

BioMarin will describe in detail the method for adjusting mannitol in the NDA application.

BioMarin will address the limits on impurities for the drug substance in the NDA application.

BioMarin had no explanation for the elevated assay result from the one-month data in study 740557.40 but, based on the testing of 30 tablets, did not believe it was indicative of a content uniformity problem. An investigation is ongoing.

BioMarin also requested that FDA provide advice on the CMC aspects of

[redacted] **FDA recommended that BioMarin submit a proposal for FDA's consideration.**

___1___ Page(s) Withheld

___✓___ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Admin / Corresp - 1

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

/s/

Brian Harvey
4/26/05 04:50:25 PM

MEMORANDUM
SERVICES

DEPARTMENT OF HEALTH AND HUMAN

Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: April 11, 2005

FROM: Jean Temeck, M.D. J Temeck 4/21/05
Acting Medical Team Leader
Division of Pediatric Drug Development, HFD-960

THROUGH: Lisa Mathis, M.D. L Mathis 4/26/05
Acting Division Director
Division of Pediatric Drug Development (DPDD, HFD-960)

TO: Brian Harvey, M.D., Ph.D.
Acting Division Director
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (DDAAODP, HFD-550)

SUBJECT: Orapred Oral Disintegrating Tablets (ODT) and PREA (PIND 70,495)

Background

BioMarin proposes to market Orapred (prednisolone sodium phosphate) ODT in 10, [redacted] and 30mg dosage strengths. They propose to cross-reference Pediapred (prednisolone sodium phosphate oral solution), NDA 19-157, for safety and efficacy and perform only a bioequivalence study. A generic product to Pediapred, Orapred (prednisolone sodium phosphate oral solution) is currently marketed.

Input from the DPDD (HFD-960) is requested from DDAAODP (HFD-550) regarding the following question from the sponsor:

"The current Orapred and Pediapred package inserts contain dosing data for the pediatric population. Does the Division agree that the information contained in these package inserts under the heading "Pediatric Use" is adequate to satisfy the need for pediatric assessment of Orapred ODT (i.e. a waiver for additional pediatric studies will be granted)?"

Review

The **Pediatric Use** section of the product labels for Pediapred and Orapred state that safety and efficacy of prednisolone in pediatric patients are based on published studies as well as extrapolation from well-controlled studies in adults in those disease states where the disease course and pathophysiology is similar between pediatric patients and adults.

The **DOSAGE AND ADMINISTRATION** sections of Pediapred and Orapred recommend a range of initial doses of 0.14-2 mg/kg/day. Pediapred contains 6.7 mg prednisolone sodium phosphate in 5cc and Orapred, 20.2 mg/5cc. Since the vehicle for both of these products is an oral solution, there is flexibility in dosing to allow administration of the lowest recommended initial dose, 0.14 mg/kg/day, to a patient of pediatric body weight. However, since with an ODT dosage form, titration of dose is not possible, and given that 10mg is the lowest ODT dosage strength, to administer a dose equivalent to 0.14 mg /kg/day, would require that the patient weigh approximately 70kg, i.e. be of adult size. Hence, for the ODT product to be applicable (relevant) to the pediatric population, a lower dosage strength than the proposed 10mg strength must be available.

Alternatively, if the Sponsor does not wish to develop a lower dosage strength of Orapred ODT, pediatric studies may be waived because there are adequate pediatric formulations already on the market, i.e. Pediapred and Orapred, that permit dosing across the entire dosing range recommended for prednisolone in pediatric patients. In addition, titration of dose is often necessary with systemic corticosteroids such as prednisolone and a fixed dosage form such as oral disintegrating tablets do not provide flexibility in dosing that is possible with the already marketed oral solutions, Pediapred and Orapred.

Conclusions and Recommendation

A bioequivalence study is sufficient to meet PREA requirements (i.e. clinical efficacy and safety studies in the pediatric population may be waived) but a lower dosage strength of the ODT formulation must be available to permit dosing across the dosing range recommended in the pediatric population for the reference listed product, Pediapred. This response was conveyed by Ms. Grace Carmouze, PM Officer, DPDD, and me in a teleconference today with HFD-550: Dr. Joel Schiffenbauer, Lead Medical Officer, and Ms. Nancy Clark, PM. It was agreed that since HFD-960 and HFD-550 were in agreement, the DPDD would not be attending the meeting with the Sponsor on Monday, April 11th.

An alternative option if the Sponsor does not wish to develop a lower dosage strength of Orapred ODT is to waive pediatric studies because the already marketed formulations

permit flexibility in dosing across the dosage range recommended for prednisolone in the pediatric population.

If pediatric studies are waived for Orapred ODT, then, as per PREA, labeling could include a statement under **PRECAUTIONS, Pediatric Use** section that this specific fixed dosage form may not be appropriate for pediatric patients.

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

/s/

Nancy Clark
9/1/2005 03:14:46 PM
CSO
Consult review is signed in ink by Drs. Temeck and Mathis

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-959	Efficacy Supplement Type SE-	Supplement Number	
Drug: ORAPRED ODT (prednisolone sodium phosphate orally disintegrating tablets)		Applicant: Medicis Pharmaceuticals	
RPM: Parinda Jani		HFD-170	Phone # (301) 796-1232

Application Type: ( ) 505(b)(1) **(X)** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Pediapred (NDA 19-157)

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	3S/5030100
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	June 1, 2006
❖ Special programs (indicate all that apply)	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number 3006144
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X)** No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (X) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	February 23, 2006

General Information	
Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	•
• Original applicant-proposed labeling	•
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	•
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	•
• Reviews	•
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	•
❖ Memoranda and Telecons	•
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary/Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	•
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	•
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	•
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	•
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	•
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	•
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	•
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: 4-10-06 **(x)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	•
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).