CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211379Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

MEMO DATE: 09/18/2019

TO: To the file for NDA 211379

FROM: Matthew D Thompson, PhD, MPH
Pharmacology/Toxicology Reviewer
Division of Hematology, Oncology, Toxicology
Office of Hematology and Oncology Products

THROUGH: Haleh Saber, PhD, MS
Deputy Division Director
Division of Hematology, Oncology, Toxicology
Office of Hematology and Oncology Products

Background

Dexcel Pharma Technologies submitted a 505(b)(2) NDA for a dexamethasone 20 mg tablet, with a broad indication for use in combination with other anti-myeloma products for the treatment of adults with multiple myeloma. The Applicant is relying on 1) FDA's findings of safety and effectiveness for Decadron (dexamethasone, NDA 011664, Merck, discontinued) and 2) the published literature in order to support labeling.

Pharmacology/Toxicology Comments

In Section 13.1 of the proposed label, the following text was added:

> Dexamethasone was tested for in vitro and in vivo genotoxic potential and was positive in the following assays: chromosomal aberrations and sister-chromatid exchanges in human lymphocytes, and micronuclei and sister-chromatid exchanges in mouse bone marrow. The Ames/Salmonella assay, with and without S9 mix, did not show an increase in His+ revertants.

This text is based on Singh et al. (1994)[1] and similar wording is found in the label of the FDA-approved product, Ciprodex (NDA 021537) under Section 13.1. Ciprodex is a combination of ciprofloxacin and dexamethasone.

[1] Singh H, Singh JR, Dhillon VS, Bali D, Paul H. In vitro and in vivo genotoxicity evaluation of hormonal drugs. II. Dexamethasone. Mutat Res. 1994 Jul 1;308(1):89-97.

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/s/

MATTHEW D THOMPSON
09/18/2019 10:50:12 AM

HALEH SABER
09/18/2019 10:51:37 AM

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	211379
Supporting document/s:	1
Applicant's letter date:	September 6, 2018
CDER stamp date:	September 6, 2018
Product:	Dexamethasone 20 mg Tablet
Indication:	In combination with other anti-myeloma products for the treatment of adults with multiple myeloma
Applicant:	Dexcel Pharma Technologies Limited
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Matthew D Thompson, PhD, MPH
Supervisor/Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD, DABT Ann Farrell, MD (DHP)
Project Manager:	Patty Garvey, RPh

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1 Executive Summary

1.1 Introduction

Dexcel Pharma Technologies submitted a 505(b)(2) NDA for a dexamethasone 20 mg tablet, with a broad indication for use in combination with other anti-myeloma products for the treatment of adults with multiple myeloma. The Applicant submitted a major amendment on June 21, 2019 to broaden the original indication. The 20 mg tablet is a new dexamethasone strength. Currently, patients typically take multiple 4 mg tablets to reach a dose of 20 or 40 mg of dexamethasone as part of an anti-multiple myeloma dosing regimen.

The Applicant is relying on 1) FDA's findings of safety and effectiveness for Decadron (dexamethasone, NDA 011664, Merck, discontinued) and 2) the published literature in order to support labeling. A nonclinical overview and summary of pharmacology and toxicology data for dexamethasone were provided by the Applicant. The Applicant did not perform nonclinical toxicology, genotoxicity, carcinogenicity, reproductive toxicity, or special toxicity studies in support of this application. The label will be based on the Decadron label with updates made to comply with the Physician Labeling Rule (PLR) and Pregnancy, Lactation, and Labeling Rule (PLLR).

Dexcel Pharma Technologies conducted a comparative bioavailability and food effect study (Study 160458) to establish a scientific bridge to the Agency's findings of safety and effectiveness for Decadron. Decadron was withdrawn from the market for reasons not related to safety or efficacy, as supported by information in the Federal Register. The Applicant sought bioequivalence to West Ward's 4 mg dexamethasone tablet (ANDA 084612) to establish the scientific bridge to Decadron.

1.2 Brief Discussion of Nonclinical Findings

The Applicant is relying on the published literature and FDA's previous findings of safety and effectiveness for Decadron. The nonclinical information in Module 4 consists of scientific literature references.

1.3 Recommendations

1.3.1 Approvability

From the pharmacology/toxicology perspective, HEMADY, a dexamethasone 20 mg tablet, may be approved for the proposed indication.

1.3.2 Additional Nonclinical Recommendations

None

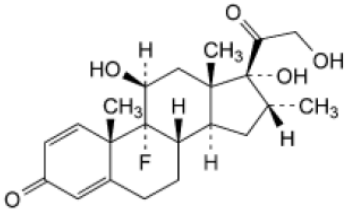
1.3.3 Labeling

At the time of this review, the labeling negotiations with the Applicant were ongoing. The nonclinical sections of the label will be based on the label of Decadron and updated to comply with PLR and PLLR.

2 Drug Information

2.1 Drug

CAS Registry Number
50-02-2
Generic Name
Dexamethasone
Chemical Name
Pregna-1,4-diene-3,20-dione,9-fluoro-11,17,21-trihydroxy-16-methyl, (11β,16α)-9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20dione
Molecular Formula/
$C_{22}H_{29}FO_5$
Molecular Weight
392.46 g/mol
Structure



(*Excerpted from Applicant's Submission*)

Pharmacologic Class
Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 011664 (Decadron, Merck, discontinued)
ANDA 084612 (West Ward, 4 mg tablet)
IND 128569 (Dexcel Pharma Technologies)
DMF (b) (4) ((b) (4)

2.3 Drug Formulation

Name of Component	Quantity per unit		Function of Component	Quality Standard
	mg	%w/w		
Dexamethasone	20.0	20.0	Therapeutic agent	USP
Lactose Monohydrate	(b) (4)		(b) (4)	NF
Corn Starch				NF
Povidone (b) (4)				USP
Sodium Starch Glycolate (b) (4)				NF
Magnesium Stearate				NF
(b) (4)				USP
Total tablet weight		(b) (4)		

(b) (4)

(*Excerpted from Applicant's Submission*)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

The Applicant conducted a single center, randomized, single-dose, open-label, 3-way crossover comparative bioavailability and food effect study to compare the rate and extent of absorption of a dexamethasone 20 mg tablet (test) versus dexamethasone 4 mg tablets, USP (Reference), administered as 1 x 20 mg or 5 x 4 mg tablets for a total dose of 20 mg fasted. The Applicant also evaluated the effect of food on the pharmacokinetic properties of dexamethasone 20 mg tablets administered as a 1 x 20 mg tablet, under fasting and fed conditions.

2.7 Regulatory Background

On March 26, 2018, the FDA granted orphan-drug designation to Dexcel Pharma Technologies for dexamethasone for treatment of multiple myeloma.

Regarding the January 2016 face-to-face meeting with the Applicant, the Agency communicated the following nonclinical comment:

Does the Agency agree that no additional non-clinical studies will be required to support marketing authorization?
FDA Response: Issues with pharmaceutical quality could necessitate additional nonclinical studies. A decision on the adequacy of the nonclinical data will be a review issue.
Discussion: The Agency clarified that the quality issues referred to in the response were regarding the presence of impurities (b) (4) For instance, if impurities are above ICHQ3A/B threshold they should be below the levels identified in the listed drug, or the levels be adequately justified.

3 Studies Submitted

None

4 Pharmacology

Not submitted

5 Pharmacokinetics/ADME/Toxicokinetics

Not submitted

6 General Toxicology

Not submitted

7 Genetic Toxicology

Not submitted

8 Carcinogenicity

Not submitted

9 Reproductive and Developmental Toxicology

Not submitted

10 Special Toxicology Studies

Not submitted

11 Integrated Summary and Safety Evaluation

See Executive Summary

12 Appendix/Attachments

None

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/s/

MATTHEW D THOMPSON
09/06/2019 02:47:40 PM

CHRISTOPHER M SHETH
09/06/2019 02:49:58 PM
I concur