CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211379Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	September 30, 2019
From	Albert Deisseroth
Subject	Division Director's Summary Review
NDA/BLA #	NDA 211379/Original-1
Applicant	Dexcel Pharma Technologies, Ltd.
Date of Submission	September 6, 2018
PDUFA Goal Date	October 6, 2019
Proprietary Name / Established (USAN) Name	HEMADY ® dexamethasone
Dosage Forms / Strength	Tablet/20 mg
Proposed Indication	Indicated in combination with other anti-myeloma products for the treatment of adults with multiple myeloma
Recommendation:	Approval

Material Reviewed/Consulted	Reviewer
CDTL Review	Nicole Gormley, MD

Associate Division Director's Summary Review

(This review was based in part on the review of the CDTL: Nicole Gormley, MD).

Background: Dexcel Pharma Technologies, Ltd. submitted NDA 211379 on September 6, 2018, in which approval was requested for the following indication for dexamethasone (Hemady): for use in combination with other anti-multiple myeloma products for the treatment of adults with multiple myeloma. No clinical data was included in the application.

Basis for Approval: As outlined in the CDTL review by Dr. Gormley, the Applicant relied on the FDA's findings of safety and efficacy for the following listed drugs: i) Decadron (dexamethasone, NDA 011664, Merck), ii) Thalomid® (thalidomide, NDA 020785, Celgene) and iii) Velcade® (bortezomib, NDA 021602, Millennium Pharmaceuticals, Inc.).

A scientific bridge was established between Hemady and the listed drug by a BA study.

As stated by Dr. Gormley in her CDTL review, the Applicant requested on June 21, 2019 an additional indication: dexamethasone is indicated in combination with other anti-myeloma products for the treatment of adults with multiple myeloma. For this indication, the Applicant relied on published literature and the Agency's previous findings of safety and efficacy for the following listed drugs:

- Decadron (dexamethasone, NDA 011664) Tablets 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg and 6 mg
- Thalomid (thalidomide) Capsules (NDA 020785)
- Revlimid (lenalidomide) (NDA 021880)
- Velcade (bortezomib) Injection (NDA 021602)
- Pomalyst (pomalidomide) (NDA 204026)
- Farydak (panobinostat) (NDA 205353)
- Ninlaro (ixazomib) (NDA 208462)
- Kyprolis (carfilzomib) (NDA 202714)

Recommended Regulatory Action: The Supervisory Associate Division Director agrees with the recommendation of the review disciplines for approval.

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/s/

ALBERT B DEISSEROTH
09/30/2019 09:23:10 AM

Cross-Discipline Team Leader Review

Date	26 Sept 2019
From	Nicole Gormley, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 211379 Original-1
Applicant	Dexcel Pharma Technologies, Ltd.
Date of Submission	6 Sept 2018
PDUFA Goal Date	6 Oct 2019
Proprietary Name / **Established (USAN) names**	HEMADY ® dexamethasone
Dosage forms / Strength	Tablet 20 mg
Proposed Indication(s)	1. Indicated in combination with other anti-myeloma products for the treatment of adults with multiple myeloma
Recommended:	Approval

Material Reviewed/Consulted	**Reviewer**
Clinical Review	Rachel Ershler, MD
Clinical Pharmacology Review	Sriram Subramaniam, PhD; Ruby Leong, PharmD
Division of Hematology and Oncology Toxicology	Matthew Thompson, PhD, MPH; Christopher Sheth, PhD
Office of Biotechnology Products	Rohit Tiwari; Su Tran; William Adams; Anamitro Banerjee; Sherita McLamore
Office of Prescription Drug Promotion	Maritsa Serlemitsos-Day, PharmD, BCPS
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Stephanie DeGraw, PharmD; Hina Mehta, PharmD

1. Introduction

On September 6, 2018, Dexcel Pharma Technologies, Ltd. (Applicant) submitted an original New Drug Application (NDA 211379) pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The proposed indication was (b) (4) Per the Applicant, in order to support the application, the Applicant intended to rely on the FDA's findings of safety and efficacy for the following listed drugs (LD): i) Decadron (dexamethasone, NDA 011664, Merck), ii) Thalomid® (thalidomide, NDA 020785, Celgene) and iii) Velcade® (bortezomib, NDA 021602, Millennium Pharmaceuticals, Inc.).

The NDA provided a new strength of dexamethasone (20 mg tablet) and a new indication, as the reference listed drug included an indication for neoplastic disease.

A scientific bridge was established between the relied-upon listed drug via a comparative bioavailability and food effect pharmacokinetic study. No new clinical data was submitted in the application.

On June 21, 2019, the Applicant submitted additional information to request a broader indication. Specifically, the Applicant requested a broader indication of dexamethasone is indicated in combination with other anti-myeloma products for the treatment of adults with multiple myeloma. To support the broader indication, the Applicant relied on published literature which described the results of clinical studies using dexamethasone in combination with anti-myeloma therapies and the Agency's previous findings of safety and efficacy for the following listed drugs:

- Decadron (dexamethasone, NDA 011664) Tablets 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg and 6 mg
- Thalomid (thalidomide) Capsules (NDA 020785)
- Revlimid (lenalidomide) (NDA 021880)
- Velcade (bortezomib) Injection (NDA 021602)
- Pomalyst (pomalidomide) (NDA 204026)
- Farydak (panobinostat) (NDA 205353)
- Ninlaro (ixazomib) (NDA 208462)
- Kyprolis (carfilzomib) (NDA 202714)

The June 21, 2019 submission was deemed a major amendment.

2. Background

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal expansion of plasma cells in the bone marrow and over-production of monoclonal immunoglobulins. The clinical features resulting from the accumulation of plasma cells or excess free light chains include hypercalcemia, renal dysfunction, anemia, bone pain and pathologic fractures, and impaired immunity.

MM is the second most common hematologic malignancy, accounting for nearly 2% of all new cancer cases and deaths. It is estimated that there will be approximately 32,110 new cases of MM and 12,960 deaths from MM in the U.S. in 2019 (American Cancer Society, Key Statistics About Multiple Myeloma). MM primarily affects older individuals, with a median age at diagnosis of 69 years (National Cancer Institute Cancer Stat Facts: Multiple Myeloma).

Significant advances have been made in the treatment of MM in recent decades with the use of high-dose therapy in combination with autologous stem cell transplantation (ASCT), and the introduction of new classes of therapeutic agents, including proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and monoclonal antibodies (mAb). In newly diagnosed patients who are eligible for ASCT, 4-year survival rates are over 80% for patients with standard-risk disease, and nearly 70% for patients with high-risk disease (Paquin, 2018).

The relied-upon listed dexamethasone has an indication for neoplastic conditions but does not mention multiple myeloma specifically. However, dexamethasone has been routinely used for the treatment of multiple myeloma for over 30 years and has been included as part of the backbone regimen for numerous FDA-approved anti-myeloma therapies. Dexamethasone is also included in multiple treatment protocols in the national comprehensive cancer network (NCCN) guidelines for multiple myeloma. Evidence suggests that dexamethasone inhibits proliferation and induces apoptosis in multiple myeloma cells in a dose dependent manner. This anti-myeloma effect is mediated via the glucocorticoid receptor and was confirmed in both multiple myeloma cells obtained from patients, as well as in well-established multiple myeloma cell lines. The safety and efficacy of dexamethasone in combination with anti-myeloma drugs is well established.

3. CMC/Device

Source: OBP Review by Drs.Tiwari, Tran, Adams, Banerjee, and McLamore.

Dexamethasone is a synthetic steroidal glucocorticoid that was approved in 1958 under the brand name Decadron (NDA 011664). Decadron was available in five strengths: 0.5, 0.75 1.5, 4 and 6 mg (withdrawn from the market in 2007). This NDA introduces a new tablet strength of dexamethasone (i.e. 20 mg vs the 6 mg highest approved strength) and a new indication (i.e. indicated for the treatment of multiple myeloma as part of combination regimens with anti-myeloma drugs).

Dexamethasone is a small chiral molecule that is manufactured by (b) (4) (b) (4) The sponsor references DMF (b) (4) for the manufacture and control of dexamethasone and includes the corresponding letter of authorization. The drug product is an immediate-release, solid, oral dosage form that is presented as a (b) (4) round, white, biconvex tablet debossed with "20" on one side.

The listed drug (Decadron) was discontinued; therefore, the sponsor conducted comparative bioavailability and in vitro dissolution studies of the drug product against West-Ward's Dexamethasone Tablets USP, 4 mg (ANDA 084612). The only difference noted between the clinical drug product and the commercial drug product is (b) (4). The clinical drug product included (b) (4) while the proposed commercial product does not. The biopharm team indicated that bridging of the clinical product to the commercial product was established based on the following:

1. dissolution profiles for clinical batches were comparable to profiles the for commercial batches under multi-media and different dissolution conditions
2. the products were manufactured at the same site
3. there were minor manufacturing process difference (b) (4)

For these reasons, it was concluded that the bridge between the clinical and commercial formulations was established and no additional in vitro or in vivo bridging studies were required.

The CMC team recommended approval of this application and granted a (b) (4) month re-test period for the drug substance when stored at (b) (4) temperature in the proposed commercial packaging.

4. Nonclinical Pharmacology/Toxicology

Source: Pharmacology/toxicology review by Drs. Thompson and Sheth.

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 nonclinical information in Module 4 consisted of scientific literature references. 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). The pharmacology/ toxicology team recommended approval.

5. Clinical Pharmacology/Biopharmaceutics

Source: Clinical Pharmacology Review by Drs. Subramaniam and Leong.

Dexcel Pharma conducted a clinical pharmacology study in healthy subjects to compare bioavailability of the proposed HEMADY 20 mg tablet to the marketed tablet formulation, and to determine effect of food on the bioavailability of HEMADY (Study 160458). Since Decadron has been discontinued, West-Ward Pharmaceuticals' 4 mg dexamethasone (ANDA 084612) tablet was used in the study. The Applicant did not conduct any other clinical studies.

The clinical pharmacology review focused on establishment of a scientific bridge between the proposed HEMADY 20 mg tablet and Decadron, demonstration of dose-PK linearity within the proposed dose range, and the appropriateness of dose recommendations for the HEMADY labeling that is based on the Decadron labeling and applicable for this indicated patient population.

The clinical pharmacology team determined that a scientific bridge was established between the listed drug and HEMADY and the dexamethasone drug products used in the literature to support the labeling recommendations. Specifically, Study 160458 demonstrated that the bioavailability of HEMADY tablet, 1 x 20 mg is comparable to the West-Ward's Dexamethasone tablet, 5 x 4 mg, in that the 90% confidence intervals (CI) of the geometric mean ratio (GMR) for primary PK parameters, Cmax, AUC0-t, and AUC0-∞ were within bioequivalence limits of 80% to 125% (Table 3: refer to Appendix 4.1 for details). In addition, the 90% CI of GMR of AUC0-t, and AUC0-∞ of HEMADY tablet, 1 x 20 mg with a high-fat meal and under fasted conditions were also within bioequivalence limits. Additionally, there were no clinically meaningful differences in AEs observed between the two formulations in the study. The Office of Clinical Pharmacology recommended approval for this NDA.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Source: Clinical Review by Dr. Ershler.

No clinical data were submitted for this NDA. In order to support the proposed indication, the Applicant is relying on the FDA's findings of safety and efficacy for Decadron, Thalomid, Velcade, Revlimid, Pomalyst, Ninlaro, Farydak and Kyprolis, as well as the published literature describing the results of clinical studies using dexamethasone in combination with these anti-myeloma drugs.

The Applicant is relying on results from a total of 20 clinical studies. Of these, five were conducted in patients with newly diagnosed multiple myeloma, and 15 were conducted in patients with relapsed or refractory multiple myeloma. Of the 20 studies, 14 are reported in the prescribing information for the following listed drugs: Thalomid, Velcade, Revlimid, Pomalyst, Farydak, Ninlaro and Kyprolis. Six additional studies are reported in the literature.

The efficacy of dexamethasone in combination with other anti-myeloma therapies is well established, and the clinical team recommends approval.

8. Safety

Source: Clinical Review by Dr. Ershler.

The safety of dexamethasone is supported by the following:

- The listed drug Decadron (NDA 011664)
- The PK study conducted for this application (Study 160458)
- Twenty Phase 2 and 3 studies that support the safety of dexamethasone in combination with anti-myeloma drugs. Of these, 14 are reported in the prescribing information for the following listed drugs: Thalomid, Velcade, Revlimid, Pomalyst, Farydak, Ninlaro and Kyprolis. Six additional studies are reported in the literature.
- Additional literature identified in the public domain that describes studies which evaluated combination regimens of dexamethasone with anti-myeloma drugs or dexamethasone as monotherapy in patients with multiple myeloma.

A total of 8006 patients with multiple myeloma have reported adverse events associated with dexamethasone in the FAERs database between 2010-2018. The patterns of adverse events reported were similar to the events reported in the clinical studies that are included in the Prescribing Information for Decadron. Most of these events were associated with dexamethasone and additional anti-myeloma drugs and are included in the labeling for these products. Collectively, the overall safety narrative and the postmarketing safety database data are similar to that described in the labeling of the listed drugs.

9. Advisory Committee Meeting

This application was not presented to the Oncologic Drugs Advisory Committee because the application did not raise significant efficacy or safety issues for the proposed indication.

10. Pediatrics

HEMADY was granted orphan designation on March 26, 2018.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No Issues
- **Financial disclosures:** In accordance with 21 CFR 54, the Applicant submitted the required financial disclosure information for investigators for the bioequivalence study.
- **Other GCP issues:** None.
- **OSI audits:** None.

There were no other outstanding regulatory issues.

12. Labeling

DMEPA, OPDP and the Division's Associate Director for Labeling participated in labeling discussions and provided recommendations.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval

- Risk Benefit Assessment

  Dexamethasone has been routinely used for the treatment of multiple myeloma for over 30 years and has been included as part of the backbone regimen for numerous FDA-approved anti-myeloma therapies. Dexamethasone is also included in multiple treatment protocols in the national comprehensive cancer network (NCCN) guidelines for multiple myeloma. The efficacy and safety of dexamethasone for the treatment of patients with multiple myeloma is well established.

  The NDA provided a new strength of dexamethasone (20 mg tablet) and a new indication, as the reference listed drug included an indication for neoplastic disease. The Applicant conducted a clinical pharmacology study in healthy subjects (Study 160458) to compare the bioavailability of the proposed HEMADY 20 mg tablet to

the marketed tablet formulation. This study established a scientific bridge between the listed drug and HEMADY and the dexamethasone drug products used in the literature to support the labeling recommendations.

Additionally, the Applicant is relying on the FDA's previous findings of safety and efficacy for Decadron, Thalomid, Velcade, Revlimid, Pomalyst, Ninlaro, Farydak and Kyprolis, as well as the published literature describing the results of clinical studies using dexamethasone in combination with these anti-myeloma drugs.

Based on the above, I recommend regular approval for HEMADY in combination with other anti-myeloma products for the treatment of adults with multiple myeloma.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  No risk management measures are recommended to support the approval of this efficacy supplement.

- Recommendation for other Postmarketing Requirements and Commitments

  No new postmarketing requirements or commitments are recommended to support the approval action for this application.

- Recommended Comments to Applicant: None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLE J GORMLEY
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