DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Jessica Chmielewski, Regulatory Affairs Associate
US Representative for Dexcel Ltd
Edenbridge Pharmaceuticals, LLC DBA Dexcel Pharma USA
1 Upper Pond Road, Suite D250
Parsippany, NJ 07054

RE: NDA 211379
HEMADY (dexamethasone tablets), for oral use
MA 33

Dear Jessica Chmielewski:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, an exhibit booth panel (exhibit panel), "Hemady Conference Banner," for HEMADY (dexamethasone tablets), for oral use (Hemady) submitted by DEXCEL Ltd under cover of Form FDA 2253. FDA also received a complaint about this exhibit panel via the FDA Bad Ad Program. This exhibit panel makes false or misleading claims and representations about the risks and benefits of Hemady. Thus, the exhibit panel misbrands Hemady within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); *Cf.* 21 CFR 202.1(e)(5). These violations are concerning from a public health perspective because the promotional communication fails to include any risk information for Hemady, a drug with multiple known serious risks, and it creates a misleading impression about the benefits of Hemady for the treatment of multiple myeloma (MM), an incurable disease whose symptoms most often recur.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Hemady.[1] According to the INDICATIONS AND USAGE section of the FDA-approved prescribing information (PI):

> HEMADY is indicated in combination with other anti-myeloma products for the treatment of adults with multiple myeloma (MM).

Hemady is contraindicated in patients with hypersensitivity to dexamethasone, or any of the excipients, and in patients with systemic fungal infections. The PI for Hemady includes warnings and precautions regarding alterations in endocrine function, immunosuppression and increased risk of infection, alterations in cardiovascular/renal function, venous and

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional communication cited in this letter.

arterial thromboembolism, vaccination, ophthalmic effects, gastrointestinal perforation, osteoporosis, myopathy, behavioral and mood disturbances, Kaposi's sarcoma, use in combination with anti-myeloma products, and embryo-fetal toxicity. The most common adverse reactions reported with Hemady are cardiovascular, dermatologic, endocrine, fluid and electrolyte disturbances, gastrointestinal, metabolic, musculoskeletal, neurological/psychiatric, ophthalmic, abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, and weight gain.

False or Misleading Risk Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to risk. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The exhibit panel is misleading because it presents efficacy claims for Hemady but fails to communicate **any** risk information. For example, the exhibit panel includes the following claims (emphasis original):

- "HEMADY® reduces up to **80%** of the number of tablets required for a therapeutic dose of dexamethasone for the treatment of adults with MM" (bolded emphasis original).
- "Hemady® is a unique strength dexamethasone tablet bioequivalent to five 4 mg tablets of dexamethasone"

The exhibit panel, however, entirely omits all risk information. By omitting the risks associated with Hemady, the exhibit panel fails to provide material information about the consequences that may result from the use of Hemady and creates a misleading impression about the drug's safety.

False or Misleading Claims about Efficacy

Promotional communications misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The exhibit panel presents a table titled "**REAL-WORLD COMPARISON OF ADHERENCE to Hemady® and generic dexamethasone among patients with MM"** (emphasis original) suggesting improved patient adherence to Hemady as compared with generic dexamethasone 4 mg tablets. Data on file[2] is cited to support the presentation. However, the referenced study does not support conclusions regarding comparative adherence to Hemady and generic dexamethasone 4 mg in the treatment of patients with MM due to limitations associated with the study design and methodology.

For example, the patient selection methodology described in the study protocol was not consistent between patients treated with Hemady and generic dexamethasone 4 mg. Specifically, according to the protocol, patients receiving Hemady were *assumed* to have been diagnosed with MM. We acknowledge that Hemady is indicated for the treatment of adults with MM. However, in contrast with patients in the generic dexamethasone 4 mg group, the study did not take measures, such as the use of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) codes,[3] to determine whether patients in the Hemady group were in fact diagnosed with MM. Relatedly, although patients in the generic dexamethasone 4 mg group were confirmed to have MM, these patients were identified for using ICD-10 CM codes that included both patients with newly diagnosed MM (NDMM) and relapsed or refractory MM (RRMM). Patients with NDMM and patients with RRMM represent distinct patient populations with varying disease severities and stages, and treatment regimens differ for each patient population. Treatment of NDMM or RRMM can involve a variable combination of multiple medications based on patient-specific factors such as tumor burden, cytogenetics, performance status, comorbidities, and eligibility for stem cell transplantation. The study protocol did not control for these or any other baseline characteristics. Further, the study protocol did not identify whether Hemady or generic dexamethasone 4 mg was used as monotherapy or as part of combination treatment regimens. These design issues can introduce bias into the adherence calculations. Moreover, factors such as the total number of medications a patient is prescribed, the number of pharmacies used, and patient age have an impact on adherence.[4] The statistical tests in this study did not control for these or any covariates.[5]

Another limitation is that the study included a significantly higher number of patients in the generic dexamethasone 4 mg group (n=3,775) compared to the Hemady group (n=43), leading to a notably unbalanced sample size. Such unbalanced sample sizes can lead to overestimation of adherence in favor of the Hemady group. Moreover, with respect to patients

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[2] Data on file (Adherence Study Results). Edenbridge Pharmaceuticals, LLC. 2023. The Data on file was provided by Edenbridge Pharmaceuticals in response to OPDP's request for the information. The study is a retrospective, comparative cohort analysis that utilized medical and pharmacy claims data to compare adherence of Hemady and generic dexamethasone in patients with MM.

[3] ICD-10-CM | Classification of Diseases, Functioning, and Disability | CDC

[4] Rajkumar, S.V., Kumar, S. (2020). Multiple myeloma current treatment algorithms. Blood Cancer Journal, 10, 94. https://doi.org/10.1038/s41408-020-00359-2

[5] Mian, H., Fiala, M., & Wildes, T. M. (2020). Adherence to Lenalidomide in Older Adults with Newly Diagnosed Multiple Myeloma. Clinical lymphoma, myeloma & leukemia, 20(2), 98–104.e1. https://doi.org/10.1016/j.clml.2019.09.618

in the dexamethasone group who may have progressed from NDMM to RRMM, the study protocol did not describe how to prevent double counting of such patients. Given these and other concerns, the results of the study do not establish improved patient adherence associated with Hemady relative to generic dexamethasone 4 mg.

Therefore, due to limitations of study design and methodology, the cited study does not support the claims regarding comparative adherence to Hemady and generic dexamethasone 4 mg among patients with MM.

Conclusion and Requested Action

For the reasons discussed above, the exhibit panel misbrands Hemady within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); *Cf.* 21 CFR 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Dexcel cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Hemady that contain representations like those described above, and explaining your plan for the timely discontinuation of such communications, or for ceasing distribution of Hemady.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 33 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6.

Additionally, the response submission should be coded as an Amendment to eCTD Sequence 0078 under NDA 211379. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Louiza Bako, PharmD
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

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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/

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