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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-785

Approval Letter(s)

HFD-540 H-11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

16 July 1998

NDA 20-785

Steve Thomas, Ph.D.
Celgene Corporation
7 Powder Horn Drive
Warren, New Jersey 07059

Dear Dr. Thomas:

Please refer to your December 20, 1996, new drug application (NDA) received on December 20, 1996, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for Thalomid (thalidomide) Capsules.

Please refer also to your "approvable" letter dated September 19, 1997. We acknowledge your submissions dated September 22, October 21 and 27, November 4 and 14, December 23 (2), 1997, January 2 (2), 7 (2), 9, 14 (2), 20, and 26, February 18, March 11 and 24, April 3 and 21, May 11 (2) and 18, June 8, and July 7, 1998. The user fee performance goal for the resubmission of this application on January 26, 1998 in response to your "approvable" letter is July 27, 1998.

This NDA provides for the use of thalidomide in the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrences.

We have reviewed this application under the restricted distribution regulations contained in 21 CFR 314 (Subpart H) and have concluded that restrictions on distribution and use of thalidomide are needed to assure safe use of the product. Please see 21 CFR 314.520.

We have completed our review of this application, including the restrictions on the distribution and use of this product you suggested in your June 8, 1998 submission to the NDA entitled "System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)." We have concluded that adequate information has now been presented to demonstrated that the drug, when marketed in accordance with the terms of restricted distribution and use outlined in the June 8, 1998 S.T.E.P.S. document, is safe and effective for use as recommended in the attached final labeling text to which you agreed on July 15, 1998 in a telephone conversation between yourself and Ms Mary Jane Walling of FDA. Accordingly, under the provisions of 21 CFR 314.520, this application is approved effective the date of this letter.

CHANGES TO THE S.T.E.P.S. RESTRICTED DISTRIBUTION PROGRAM:

Please note that the June 8, 1998 S.T.E.P.S. restricted distribution program is an integral part of the approved NDA for this product and is an essential component of the terms of this NDA's approval by FDA for marketing this product in the United States. As such, any proposed change(s) in the S.T.E.P.S. program must be submitted to the FDA as a supplement to this NDA and any proposed change(s) must have FDA prior approval before implementation. Changing the S.T.E.P.S. program without prior FDA approval may render the product misbranded and an unapproved new drug.

FINAL PRINTED LABELING:

The final printed labeling (FPL) for this product must be identical to the attached approved final labeling text, including the two informed consent documents (one for male patients and one for female patients); the authorization document; and the boxes, bolding, bullets, and other formatting provisions. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit twenty copies of the FPL as soon as it is available; however, in no case should it be submitted more that thirty days after it is printed. Please individually mount ten copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designed "FINAL PRINTED LABELING for approved NDA 20-785." Approval of this submission by FDA is not required before the labeling is used.

FUTURE INSPECTIONS:

In order to monitor the success of compliance with the restricted distribution provisions of this approval action, we intend to conduct inspections of the monitoring sites, i.e., the [ ], as well as Celgene's records during the first quarter after product launch. We will meet with you to discuss the inspections within one month after completions of the inspections. Inspections and meetings with you will continue periodically thereafter as appropriate.

SPECIAL ADVERSE EVENT REPORTING REQUIREMENT:

Please note that, until further notice, **ALL** reports you receive of a possible human fetal exposure to this drug in the United States or of a possible human congenital malformation(s)

following exposure to this drug in the United States must be reported to the FDA as "serious, unexpected" adverse events, (i.e., within 15 calendar days of your receipt of the report.)

PHASE FOUR COMMITMENTS:

Please be reminded of your Phase 4 commitments specified in your submission dated July 7, 1998. These commitments, along with any completion dates agreed between Celgene and FDA, are listed below:

1. Ongoing Study E003/P for efficacy should be continued and efforts should be made to expand the population in order to accrue the full compliment of subjects, as stated in our letter to you dated May 12, 1998.

2. To conduct studies to demonstrate the absence or presence of thalidomide in sperm and / or semen.

3. To conduct rat and mouse carcinogenicity studies.

4. To conduct a segment I reproductive toxicity study in rabbits.

5. To conduct a segment III reproductive toxicity study in rabbits.

6. To develop and propose a component qualification test/specification for the packaged drug product that will verify the integrity of the blister pack with respect to moisture vapor transmission. This should not be considered to be a regulatory specification. This commitment should be completed in six months.

7. To submit the results of release testing results for lots 0091N, 0092N and 0149N, along with updated stability data for lots DEV 2775, 2800 and 2811, as well as release data for lots 0091N, 0092N and 0149N. These results along with previously submitted data on the drug substance will be used to evaluate the bulk drug and finished product specifications. The timely submission and review of the results of ongoing stability testing of lots 0091N, 0092N and 0149N will determine if a [ ] expiration period will be granted.

8. To develop and propose a component qualification test/specification for the packaged drug product that will verify the integrity of the blister pack with respect to moisture vapor transmission. This should not be considered to be a regulatory specification. This commitment should be completed in one year.

9. There also remain two outstanding commitments described in our letter of September 19, 1997. They are numbers 5(a) and 5 (e). Please provide these data when available.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

PROMOTIONAL ACTIVITIES:

Please note that promotional activities for this approved NDA are subject to 21 CFR 314.550. As such, please submit three copies of the introductory promotional materials you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit two copies of both the promotional material and the final printed labeling or approved final labeling text to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

In addition, please note that this product has been approved **ONLY** for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. It is not approved as monotherapy for the treatment of ENL cutaneous manifestations in the presence of moderate to severe neuritis. In addition, the safety and efficacy of this product in the treatment of any manifestations of HIV-associated disease were not addressed and thus have not been demonstrated in the data you submitted to this NDA. Statements in the approved labeling for this product that refer to HIV seropositive

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