

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-785

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

HFD-540 411

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 demonstrate 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.

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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 than 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)

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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.

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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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patients are included in the approved labeling ONLY to provide further safety information to the prescriber. Their inclusion is not intended to imply that use of your product is approved in this population of patients. As such, please note that statements or implications by you that this product may indeed be safe and efficacious in the treatment of diseases or patient populations beyond that approved in your application may be considered a violation of the promotional provisions of the Act. If you have any questions or concerns about this matter, please contact the Center for Drug Evaluation and Research's Division of Drug Marketing, Advertising, and Communications.

CHEMISTRY:

Our validation of the chemistry testing methods has not been completed at this time. Presently, it is the general policy of the Center not to withhold approval for an application because these methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

MISCELLANEOUS:

Please submit one marketing package of the drug product when it is available.

Please note that, with this approval action, the oversight of this NDA (20-785) and IND 48, 177 is being transferred to the Division of Special Pathogens and Immunologic Drug Products, HFD-590. This transfer is being effected because HFD-590 is the division that now has primary oversight of immunomodulatory drug products and of products whose purpose is to treat diseases caused by mycobacteria. The product covered by NDA 20-785 and IND 48,177 clearly meets both of these criteria. As such, it is most appropriate that it now be overseen by HFD-590.

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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80, 314.81, 314.520, 314.550, and 314.560.

If you have any questions regarding this NDA, please contact Mary Jane Walling, Project Manager, at (301) 827-2268.

Sincerely,

A handwritten signature in cursive script that reads "Murray M. Lumpkin". The signature is written in dark ink and is positioned above the typed name.

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

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HFD-2/Lumpkin

HFD-105/CSO/Walling

HFD-590/Dir/Goldberger

HFD-530/MO/Birnkrant

HFD-540/Chem/DeCamp

HFD-540/Tox/Hill

HFD-550/Biopharm/Bashaw

HFD-95/DDM-DIAB(with labeling)

DISTRICT OFFICE

HFD-232

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

HFI-20/Press Office (with labeling)

HFD-021/ACS (with labeling)

HFD-830/ONDC/DD

DRAFTED:MJWALLING:06/01/98

REVISED:MJWALLING:07/06/98:7/10/98

APPROVAL (AP)

with Phase 4 commitments

CENTER FOR DRUG EVALUATION AND RESEARCH

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 19 1997

NDA 20-785

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

Dear Dr. Thomas:

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

We acknowledge receipt of your submissions dated October 24, 1996; and January 20, 23 and 28, February 3 and 25, March 6 and 7, April 1 and 25, May 23, June 2, 12, 16, and 17, July 16 (two) and 25, August 1, 12, 18, 21, 26, 27, and 29 (two), and September 2, 1997. The original User Fee goal date for this application was June 20, 1997. Your submission of June 16, 1997 extended the User Fee goal date to September 20, 1997.

We have completed the review of this application as submitted, including restrictions on distribution and use as stated in the NDA, and it is approvable. We have reviewed this application under the Accelerated Approval Regulations contained in 21 CFR 314 (Subpart H) and have concluded that the restriction on distribution and use of thalidomide are needed for safety. (See 21 CFR 314.520) We expect that the restrictions under Subpart H will be agreed to in writing by both the FDA and Celgene.

Before this application may be approved, however, we will need to reach agreement on the wording of the final labeling this product will have and on the specific details of the elements of the restricted distribution and educational programs for the product. Therefore, please resubmit draft final labeling and details of your restricted distribution and educational program incorporating suggestions from the Advisory Committee meeting of September 4 and 5, 1997 and from the FDA. In addition, please submit data demonstrating that the program will meet its stated goals.

Issues surrounding the potential "scheduling" of thalidomide under the provisions of the Controlled Substances Act will also need to be resolved prior to approval.

In addition, before this application may be approved, it will be necessary for you to address the

following issues:

1. Please submit an amendment to adopt the tighter specifications of [] for the assay of bulk thalidomide. This amendment should also indicate if any lots of bulk drug have been released for manufacturing with assay results outside these limits.
2. Please provide the following additional information as either revisions of or clarifications to your analytical methods as follows:
 - (a) Celgene Method SOP-121 (Thalidomide Assay) should be clarified to state what "Sample A" and "Sample B" are, to include approximate retention times for all peaks of interest, to define the peaks between which resolution is measured, and to provide a rationale for specifying two detector wavelengths ([]), only one of which appears to be used;
 - (b) Celgene Method SOP-122 (Related Impurities) should be clarified to define the calculation basis for the relative retention time, to provide a rationale for specifying two detector wavelengths ([]), and to be more specific about the retention times of the impurities to be calculated;
 - (c) Celgene Method SOP-120 (Dissolution) and Celgene Method SOP-128 (Content Uniformity) should be clarified as described for Method 121.
3. Based on our statistical review of the data submitted, we have concluded that the maximum expiration dating that can be justified at this time is eighteen months for thalidomide. Please request an adjustment of the maximum expiration date to eighteen months.
4. []
 - (a) []
 - (b) []
 - (c) []

[]

5. We request that the following studies be conducted as Phase 4 commitments:

- []
-]
- (a) The potential of thalidomide to accumulate in fatty tissue depends upon its solubility in lipid containing tissues and lipophilic media. Please provide a commitment to perform a study in animals to determine tissue levels. This study should also include a determination of the octanol-water partition coefficient. Please report your findings within 120 days following the date of this letter.
 - (b) A study should be done with thalidomide given at night to insure that diurnal factors are not interfering with pharmacokinetics.
 - (c) We remind you of your commitment to do a two way cross-over study of oral solution versus marketed product. This study has been called PK007.
 - (d) In addition, you have agreed to make the following changes to the protocol for E003/P:
 - I. Monitoring blood pressures and pulse while the patients are standing and sitting and at the time of peak drug levels.
 - ii. Oral and axillary temperatures are both to be measured. Fever severity should be noted in temperature ranges.
 - iii. Information should be recorded about the concomitant use of aspirin, non-steroidal anti-inflammatory drugs and acetaminophen.
 - iv. Actual lesion counts should be performed.

- v. Severity parameters for ENL lesions should be clearly defined, standardized, and used.
- vi. We suggest that the term "not present" or similar term(s) be used to denote that an assessment has been made and the particular symptom is not present.
- vii. We suggest that clinical assessment should be performed on a weekly basis after the first week.
- viii. It was noted in animal tests that the color of the urine changed. As part of the standard urinalysis, please note color.

- (e) Additional solubility information should be obtained and reported not later than the first Annual Report. This should include the equilibrium aqueous solubility in the pH range of 1-9 and the equilibrium solubility as a function of temperature in [] over the temperature range typically used for recrystallization.

6. The Labeling and Nomenclature Committee has judged the name "Synovir" unacceptable. They noted numerous potential look-alike/sound-alike conflicts with SYNACORT, SYNALAR, SYNEMOL, SINEQUAN, SINEMET and CINOBAC. Additionally, "-vir" is the USAN stem reserved for anti-viral products and this product is not a pending anti-viral product. Therefore if you intend to use a trade name for this product please submit a new proposed name.

Although not the basis for the approvability of this application, the following issues should be addressed in your resubmission:

- 1. We recommend initiation of accelerated stability studies for bottles of 14, 28, 56, and appropriate multiples of 56 capsules as being more consistent with anticipated clinical usage. An appropriate amendment or supplement should be submitted on the completion of three months stability study.
- 2. We encourage you to continue efforts to develop an improved non-destructive assay for []
- 3. We request that you submit additional information concerning the historical control data for CD-1 mice and the formation of corneal crystals. In addition, it would be helpful for you to provide a potential explanation for: a) the formation of cataracts in the 14 day repeat dose toxicity study and not in the 90 day repeat dose toxicity study performed in mice and b) the formation of corneal crystals in the 90 day repeat dose toxicity study and not in the 14 day repeat dose toxicity

study performed in mice.

4. There were two neoplasms observed in the 13 week repeat dose toxicity study performed in CD-1 mice. A low dose male had a small alveolar-bronchiolar adenoma involving the lung and a high dose female had a uterine stromal polyp. Tumor findings are quite uncommon in a 13 week repeat dose toxicity study. It may be true that the two types of observed tumors are relatively common spontaneous neoplasms in CD-1 mice, but one would anticipate that these tumors are relatively uncommon in CD-1 mice at this early a time in their life span. We request that you submit additional information on the historical control data for CD-1 mice to validate the claim that the two types of tumors observed in this study are relatively common spontaneous neoplasms in CD-1 mice. In particular, please pay special attention to clarifying at what time point in the life span of the CD-1 mice are alveolar-bronchiolar adenomas and uterine stromal polyps observed and what is their frequency level. One potential possibility for the presence of the alveolar-bronchiolar adenoma could be due to a murine virus infection of that particular animal. We request that you provide additional information on the health status of the CD-1 mice used in this 13 week repeat dose toxicity study.
5. We are concerned about the AUC values obtained in the 52 week repeat dose toxicity study in dogs. The maximum AUC obtained in this study (approx. 100 $\mu\text{g}\cdot\text{hr}/\text{ml}$) is substantially lower (approx. $\frac{1}{4}$ X) than was obtained in the 7 day repeat dose pharmacokinetics study (approx 400 $\mu\text{g}\cdot\text{hr}/\text{ml}$) performed in dogs. We request that you submit any additional information that you may have to provide an explanation for this observation. In particular, information concerning the status of the dogs fed or fasted state prior to dose administration would be quite useful. In dogs, the pH in the stomach varies according to how recently the dogs have eaten and this could have a dramatic effect on the rate of spontaneous hydrolysis of thalidomide.
6. We are concerned about the stability of thalidomide (due to spontaneous hydrolysis) under the assay conditions for the *in vitro* genetic toxicology studies that investigated the potential for thalidomide to induce mutations. It is unclear as to the stability of thalidomide in the media used to conduct the two *in vitro* genetic toxicology studies. We request that you submit information about the stability of thalidomide under the conditions of the two *in vitro* genetic toxicology studies conducted for thalidomide. We recommend that you make the following modifications to the two carcinogenicity (rat and mouse) protocols: a) delete the clinical pathology assessment at week 104 due to these results may be confounded by age related toxicities, b) draw blood from a

satellite group of mice (not the animals to be used for the main study) for the week 54 clinical pathology assessment, and c) conduct histopathological examination of all of the tissues from all of the dose groups in both carcinogenicity assays.

7. We recommend that you resubmit the two carcinogenicity (rat and mouse) protocols with the results of their respective 90 day dose range studies to support the dose selection for these studies. Please be advised that the two carcinogenicity protocols, along with their respective 90 day dose range studies, will be submitted to the executive Carcinogenicity Assessment Committee (CAC) for evaluation and recommendations. The recommendations from the executive CAC evaluation of the two carcinogenicity protocols will be shared with you.
8. We recommend that you include full hematological and clinical chemistry profile measurements in both of the reproductive toxicity dose range finding studies in male and female rabbits at appropriate time points in this study (i.e., day 7 and study termination). We recommend that you evaluate mating performance in the reproductive toxicity dose range finding study in male rabbits.
9. We recommend that you evaluate mating performance in the Segment I reproductive toxicity study in rabbits.
10. We recommend that you evaluate a measure of sexual maturation in the Segment III reproductive toxicity study in rabbits. It is also recommended that you evaluate some parameters of development in this study (i.e., measurements of learning capacity, physical strength, and motor coordination).
11. We recommend that you resubmit the Segment I and III reproductive toxicity protocols after completion of the reproductive toxicity dose range finding studies to support the dose selection for these studies.
12. You have yet to fulfill your commitment made in the protocol to analyze fecal samples collected during study PK-005. Please provide a time frame for doing so.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all additional safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.
2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Provide details of any significant changes or findings, if any.
4. Summarize worldwide experience on the safety of this drug beyond that which was included in your NDA.
5. Submit case report forms for each patient who died during clinical studies E001 and E003/P or who did not complete either one of these two studies because of an adverse event.

Please also update the new drug application with respect to new reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please be advised that the regulations at 21 CFR 314.550 regarding promotional materials for products approved under Accelerated Approval (Subpart H) will apply to this product. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

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

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

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Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Office to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Mary Jane Walling at (301) 827-2268.

Sincerely yours,

M Weintraub 9/19/97

Michael Weintraub, M.D.

Director

Office of Drug Evaluation V

Center for Drug Evaluation and Research