CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-954/S-004

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-954/S-004

Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

Attention: Carol S. Curme, J.D., R.A.C.
Senior Manager of Regulatory Affairs

Dear Ms. Curme:

Please refer to your supplemental new drug application dated December 12, 2001, received December 28, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Busulfex® (busulfan) Injection.

We acknowledge receipt of your submissions dated July 22, November 6, and December 13, 2002.

Your submission of July 22, 2002 constituted a complete response to our June 28, 2002 action letter.

This supplemental new drug application proposes a change to the package insert for Busulfex® (busulfan) Injection by incorporating pediatric information on dosing, pharmacokinetics and safety.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-954/S-004." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sean Bradley, R.Ph., Regulatory Project Manager, at (301) 594-5770.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
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Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-954/S-004

Orphan Medical, Inc.
13911 Ridgedale Dr.
Suite 250
Minnetonka, MN 55305

Attention: Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs

Dear Ms. Curme:

Please refer to your supplemental new drug application dated December 21, 2001, received December 28, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Busulfex® (busulfan) Injection.

We acknowledge receipt of your submissions dated January 11; February 14, 15, and 25; April 22; May 6, and 22; June 6 and 17, 2002.

This supplemental new drug application proposes a change to the package insert for Busulfex® (busulfan) Injection by incorporating pediatric information on dosing, pharmacokinetics and safety.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information regarding your approach to therapeutic drug monitoring:

1. Justify the choice of the 2, 4 and 6 hour times for sampling Busulfex concentrations.
2. Demonstrate that the use of these three samples can accurately determine AUC. You should provide a comparison of the Busulfex AUC derived from the complete data for each patient in the OMC-BUS-5 with the AUC derived using the three samples at the proposed time points for each patient.
3. Provide Busulfex labeling instructions that explain how to take the samples and how to calculate the AUC.

It will be necessary for you to submit draft labeling revised to reflect the information requested above.

All previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental 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 any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Sean Bradley, R.Ph., Regulatory Health Project Manager, at 301-594-5750.

Sincerely,

{See appended electronic signature page}

/S/

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
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