CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-954

STATISTICAL REVIEW(S)

Statistical Review

The review of this application was a joint review with the Medical Officer. Please see the Medical Review for Recommendation.

Statistical Review and Evaluation

NDA #: 20-954

JAN 7 1999

Applicant: Orphan Medical

Name of Drug: Busulfex (busulfan) Injection

Indication: Conditioning regimen for hemotopoietic progenitor cell transplantation

Document Reviewed: Volume 1.22, dated 29 Jul 98

The sponsor submitted an IV Busulfan multivariate analysis report but there were two questions regarding the statistical analysis that required a statistical consultation.

Question 1: Was clearance normalized to adjusted ideal body weight or body surface area significantly different among lean, normal, obese, and severely obese patients?

Question 2: Is there sufficient evidence to support the claim that dosing does not require adjustment for gender or race?

Statistical Reviewer's Comments

Question 1: The analysis that was presented in the submission was appropriate and had sufficient power to conclude that clearance normalized to adjusted ideal body weight or body surface area was not significantly different among lean, normal, obese, and severely obese patients. However, there were differences among the four groups of patients with respect to *absolute clearance*, *adjusted body weight*, and *ideal body weight*. For absolute clearance, normal and obese patients were statistically significantly different. For adjusted body weight, severely obese patients were statistically significantly different than each of the following groups: lean, normal and obese patients. For ideal body weight, normal and obese patients were statistically significantly different.

Question 2: There is insufficient evidence presented in the results presented to conclude that dosing does not require adjustment for gender or race. Although this analysis was performed (based on its description in the study report), the specific regression results that show that gender and race were not statistically significant were not included in the submission.

/S/

David Smith, Ph.D.
Mathematical Statistician

Concur: Dr. Chen /S/ 1/7/99

Dr. Chi /S/ 1/7/99

cc:

Archival IND
HFD-150/Dr. Rahman
HFD-150/Dr. Booth
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Smith
HFD-710/Chron
HFD-710/Mr. Guinn

SMITH / 11 Dec 98 / WordFiles / busulfanconsult.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-954

MICROBIOLOGY REVIEW(S)

HFD-150/ Quinn

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review #1 of NDA 20-954 JAN 14 1999
January 13, 1999

A. 1. **APPLICATION NUMBER:** 20-954

APPLICANT: Orphan Medical, Inc.
13911 Ridgedale Drive
Suite 475, Minnetonka
Minnesota 55305

2. **PRODUCT NAMES:** Busulfex (busulfan) Injection

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** A sterile liquid of 60 mg of busulfan in each ampoule. The fill volume is 10 ml. Busulfex is for single use and it is to be administered intravenously.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** 1P orphan drug. Use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation.

B. 1. **DATE OF INITIAL SUBMISSION:** August 3, 1998

2. **AMENDMENT:** Minor Amendment: December 11, 1998

3. **RELATED DOCUMENTS:** Fax Response: January 11, 1999

4. **ASSIGNED FOR REVIEW:** September 2, 1998

5. **DATE OF CONSULT REQUEST:** August 18, 1998

C. **REMARKS:**

Busulfex Injection is supplied as a sterile solution in 10 ml single use clear glass ampoules each containing 60 mg of busulfan at a concentration of 6 mg/ml for intravenous use. The drug product is manufactured by Ben Venue Laboratories in Bedford, Ohio.

D. CONCLUSIONS:

The submission is recommended for approval on issues concerning sterility assurance.

/S/ : 1/13/98

Brenda Uratani, Ph.D.
Review Microbiologist

PHC 1/14/99

cc:

NDA 20-954
HFD-150/ Div. File
HFD-805/ Uratani
HFD-150/Guinn
drafted by: Brenda Uratani, 1/13/98
R/D initialed by P. Cooney, 1/13/98