CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-954

CHEMISTRY REVIEW(S)
Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-954

SUBMISSION TYPE
Original
BC
BC
BC
Fax Amendment

DOCUMENT DATE
Aug. 3, 1998
Oct. 20, 1998
Dec. 8, 1998
Jan. 15, 1999
Jan. 25, 1999
Jan. 28, 1999

CDER DATE
Aug. 4, 1998
Oct. 21, 1998
Dec. 9, 1998
Jan. 15, 1999
Jan. 25, 1999
Jan. 28, 1999

ASSIGNED DATE
Aug. 7, 1998
Oct. 26, 1998
Dec. 11, 1998
Jan. 15, 1999
Jan. 25, 1999
Jan. 28, 1999

NAME AND ADDRESS OF APPLICANT:
Orphan Medical, Inc.
13911 Ridgedale drive, Suite 475
Minnetonka, MN 55305

DRUG PRODUCT NAMES:
Proprietary:
Busulfex™ Injection

Nonproprietary/USAN:
Busulfan

Code Name/#
CAS 55-98-1
3-P

PHARMACOL. CATEGORY/INDICATION:
Use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation.

DOSAGE FORM/STRENGTHS:
10mL (6mg/mL)

ROUTE OF ADMINISTRATION:
Intravenous

MANUFACTURER:
A. Drug Substance
Ash Stevens, Inc.
5861 John C. Lodge Freeway
Detroit, MI 48202

B. Drug Product
Ben Venue Laboratories, Inc.
270 Northfield road
P.O. Box 46568
Bedford, OH 44146-0568

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:
1,4-butanediol-dimethanesulfonate esters

Supporting Documents:

DMF

Acceptable

acceptable

DMF

Acceptable
DMF

Acceptable.

Acceptable

Acceptable.

IND

Acceptable.

**CONSULTS:**

<table>
<thead>
<tr>
<th>Consult</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consult</td>
<td>Complete</td>
<td>Acceptable recommended by the Office of Compliance on 10/19/98</td>
</tr>
<tr>
<td>EER</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Methods Validation**

Pending

Will be submitted after the NDA approval

**Trademark**

Complete

Acceptable

Refer to Dr. Dan Boring’s email dated 1/21/99

**Pharma/Tox**

Complete

Acceptable

Reviewed by Dr. McGuinn on 2/1/99

**Microbiology**

Complete

Acceptable

Reviewed by Dr. Brenda Uratani on 1/13/99

**Environmental Assessment.**

Categorical exclusion

Acceptable

**REMARK/COMMENTS:**
The drug substance and the drug product deficiencies have been addressed in the fax amendment dated Jan. 29, 1999. There are a number of Phase IV commitment that the applicant has furnished.

**CONCLUSIONS AND RECOMMENDATIONS:**
This NDA is recommended for approval.
Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-954

SUBMISSION TYPE
Original
BC
BC
BC
BC

DOCUMENT DATE
Aug. 3, 1998
Oct. 20, 1998
Dec. 8, 1998
Jan. 15, 1999
Jan. 25, 1999

REVIEW DATE: Jan. 28, 1999

CDER DATE
Aug. 4, 1998
Oct. 21, 1998
Dec. 9, 1998
Jan. 15, 1999
Jan. 25, 1999

ASSIGNED DATE
Aug. 7, 1998
Oct. 26, 1998
Dec. 11, 1998
Jan. 15, 1999
Jan. 25, 1999

NAME AND ADDRESS OF APPLICANT:
Orphan Medical, Inc.
13911 Ridgedale drive, Suite 475
Minnetonka, MN 55305

DRUG PRODUCT NAMES:
Proprietary:
Busulfex™ Injection

Nonproprietary/USAN:
Busulfan

Chem. Name/#:
CAS 55-98-1

Chem. Type/Ther. Class
3-P

PHARMACOL. CATEGORY/INDICATION:
Use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation...

DOSAGE FORM/STRENGTHS:
10mL (6mg/mL)

ROUTE OF ADMINISTRATION:
Intravenous

MANUFACTURER:
A. Drug Substance
Ash Stevens, Inc.
5861 John C. Lodge Freeway
Detroit, MI 48202

B. Drug Product
Ben Venue Laboratories, Inc.
270 Northfield road
P.O. Box 46568
Bedford, OH 44146-0568

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:
1,4-butanediol-dimethanesulfonate esters

C₈H₁₄O₂S₂, MW = 246.31

CH₂- S- O- CH₂- CH₂- CH₂- CH₂- CH₂- O- S- CH₃

SUPPORTING DOCUMENTS:
DMF
Acceptable

DMF
acceptable

DMF
Acceptable
DMF acceptable.

DMF

Acceptable

DMF acceptable.

IND acceptable.

CONSULTS:
Consult
EER

Methods Validation

Trademark

Pharma/Tox

Microbiology

Environmental Assessment.

Status
Complete
Pending
Complete
Pending
Complete
Categorical exclusion

Comments
Acceptable recommended by the Office of Compliance on 10/19/98
Will be submitted after the deficiencies have been addressed by the applicant
Acceptable
Refer to Dr. Dan Boring's email dated 1/21/99
Submitted on 9/21/98
Acceptable
Reviewed by Dr. Brenda Uratani on 1/13/99
Acceptable

REMARK/COMMENTS:
There are a number of deficiencies related to the drug substance and the drug product. The deficiencies were conveyed to the applicant before and during three teleconferences that were held on Jan. 22 and 27, 1999 to discuss the CMC comments and deficiencies. The applicant has agreed to our concerns and deficiencies, they will submit their responses to the Agency.

CONCLUSIONS AND RECOMMENDATIONS:
This NDA cannot be approved until their responses are received and reviewed.
Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-954
CHEM. REVIEW#: 3
REVIEW DATE: Jan. 20, 1999

SUBMISSION TYPE
Original
BC
BC
BC

DOCUMENT DATE
Aug. 3, 1998
Oct. 20, 1998
Dec. 8, 1998
Jan. 15, 1999

CDER DATE
Aug. 4, 1998
Oct. 21, 1998
Dec. 9, 1998
Jan. 15, 1999

ASSIGNED DATE
Aug. 7, 1998
Oct. 26, 1998
Dec. 11, 1998
Jan. 15, 1999

NAME AND ADDRESS OF APPLICANT:
Orphan Medical, Inc.
13911 Ridgedale drive, Suite 475
Minnetonka, MN 55305

DRUG PRODUCT NAMES:
Proprietary: Busulfex™
Nonproprietary/USAN: Injection Busulfan
Code Name/#: CAS 55-90-1
Chem. Type/Ther. Class 3-P

PHARMACOL. CATEGORY/INDICATION:
Use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation...

DOSAGE FORM/STRENGTHS:
10mL (6mg/mL)

ROUTE OF ADMINISTRATION:
Intravenous

MANUFACTURER:
A. Drug Substance
Ash Stevens, Inc.
5861 John C. Lodge Freeway
Detroit, MI 48202

B. Drug Product
Ben Venue Laboratories, Inc.
270 Northfield road
P.O. Box 46568
Bedford, OH 44146-0568

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:
1,4-butanediol-dimethanesulfonate esters
C₆H₁₄O₅S₂, MW = 246.31

SUPPORTING DOCUMENTS:
DMF
Acceptable

DMF
acceptable

DMF
Acceptable
CONSULTS:
Consult  Status  Comments
EER    Complete  Acceptable recommended by
Methods Validation  Pending  the Office of Compliance on 10/19/98
Trademark  Pending  Will be submitted after
Statistics  Pending  the deficiencies have been
Pharma/Tox  Pending  addressed by the applicant
Microbiology  Complete  Submitted on 9/21/98
Environmental Assessment  Categorical  Accepted
exclusion  Reviewed by Dr. Brenda
Urata on 1/13/99

REMARK/COMMENTS:
Drug Substance: There are a number of deficiencies related to the drug
substance. The deficiencies are conveyed to the applicant and they should be
addressed before this NDA can be approved.

Drug Product: There are quite a few deficiencies related to drug product
section. They need to be addressed before approval is recommended.

CONCLUSIONS AND RECOMMENDATIONS:
This NDA cannot be approved until all the CMC deficiencies are satisfactorily
addressed and pending consults are completed.
Xiao Hong Chen, Ph.D., Review Chemist

Nallaperumal Chidambaram, Ph.D.
Review Chemist

Liang Zhou, Ph.D.
Chemistry Team Leader

CC:
Orig. NDA 20-954
HFD-150 Division File
HFD-150/XChen
HFD-150/NChidambaram
HFD-150/LZhou
HFD-150/PGuinn
HFD-810/Directors
Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-954     CHEM. REVIEW#: 2     REVIEW DATE: Jan. 8, 1999

SUBMISSION TYPE
Original
BC
BC

DOCUMENT DATE
Aug. 3, 1998
Oct. 20, 1998
Dec. 8, 1998

CDER DATE
Aug. 4, 1998
Oct. 21, 1998
Dec. 9, 1998

ASSIGNED DATE
Aug. 7, 1998
Oct. 26, 1998
Dec. 11, 1998

NAME AND ADDRESS OF APPLICANT:
Orphan Medical, Inc.
13911 Ridgedale drive, Suite 475
Minnetonka, MN 55305

DRUG PRODUCT NAMES:
Proprietary: Busulfex™ Injection
Nonproprietary/USAN: Busulfan
Code Name/#: CAS 55-98-1
Chem. Type/Ther. Class 3-P

PHARMACOL. CATEGORY/INDICATION:
Use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation...

DOSAGE FORM/STRENGTHS:
10mL (6mg/mL)

ROUTE OF ADMINISTRATION:
Intravenous

MANUFACTURER:
A. Drug Substance
Ash Stevens, Inc.
5861 John C. Lodge Freeway
Detroit, MI 48202

B. Drug Product
Ben Venue Laboratories, Inc.
270 Northfield road
P.O. Box 46568
Bedford, OH 44146-0568

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:
1,4 -butanediol-dimethanesulfonate esters
\( \text{C}_8\text{H}_{14}\text{O}_4\text{S}_2, \text{MW} = 246.31 \)

SUPPORTING DOCUMENTS:
DMF

acceptable
DMF
DMF
acceptable.

DMF

acceptable.

DMF

IND

CONSULTS:

<table>
<thead>
<tr>
<th>Consult</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EER</td>
<td>Complete</td>
<td>Acceptable recommended by the Office of Compliance on 10/19/98</td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Pending</td>
<td>Will be submitted after the deficiencies have been addressed by the applicant</td>
</tr>
<tr>
<td>Trademark</td>
<td>Pending</td>
<td>Submitted on 1/7/97</td>
</tr>
<tr>
<td>Statistics</td>
<td>Pending</td>
<td>Submitted on 9/10/98</td>
</tr>
<tr>
<td>Pharma/Tox</td>
<td>Pending</td>
<td>Submitted on 9/21/98</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Pending</td>
<td>Submitted on 8/18/98</td>
</tr>
<tr>
<td>Environmental Assessment</td>
<td>Categorical exclusion</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>

REMARK/COMMENTS:
Drug Substance: There are a number of deficiencies related to the drug substance. The deficiencies are conveyed to the applicant and they should be addressed before this NDA can be approved.

Drug Product: There are quite a few deficiencies related to drug product section. They need to be addressed before approval is recommended.

CONCLUSIONS AND RECOMMENDATIONS:
This NDA cannot be approved until all the CMC deficiencies are satisfactorily addressed and pending consults are completed.

/S/ 1/8/99
Xiao Hong Chen, Ph.D., Review Chemist
Nallaperumal Chidambaram, Ph.D.
Review Chemist

Liang Zhou, Ph.D.
Chemistry Team Leader

CC:
Orig. NDA 20-954
HFD-150 Division File
HFD-150/XChen
HFD-150/NChidambaram
HFD-150/LZhou
HFD-150/PGuinn
HFD-810/Directors
Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 20-954  CHEM. REVIEW#: 1  REVIEW DATE: Nov. 30, 1998

SUBMISSION TYPE  DOCUMENT DATE  CDER DATE  ASSIGNED DATE

NAME AND ADDRESS OF APPLICANT:
Orphan Medical, Inc.
13911 Ridgedale drive, Suite 475
Minnetonka, MN 55305

DRUG PRODUCT NAMES:
Proprietary:  Busulfex™ Injection
Nonproprietary/USAN:  Busulfan
Code Name/#:  CAS 55-98-1
Chem. Type/Ther. Class:  3-P

PHARMACOL. CATEGORY/INDICATION:
Use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation.

DOSAGE FORM/STRENGTHS:
10mL (6mg/mL)

ROUTE OF ADMINISTRATION:
Intravenous

MANUFACTURER:
A. Drug Substance  B. Drug Product
Ash Stevens, Inc.  Ben Venue Laboratories, Inc.
5861 John C. Lodge Freeway  270 Northfield road
Detroit, MI 48202  P.O. Box 46568

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:
1,4-butanediol-dimethanesulfonate esters

\[ \text{C}_6\text{H}_{14}\text{O}_4\text{S}_2, \text{ MW = 246.31} \]

\[ \text{CH}_3 \quad \text{O} \quad \text{S} \quad \text{O} \quad \text{CH}_3 \quad \text{CH} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH} \quad \text{O} \quad \text{S} \quad \text{CH} \]

SUPPORTING DOCUMENTS:

DMF

DMF

DMF

DMF

acceptable.
DMF

DMF

DMF

IND

CONSULTS:

<table>
<thead>
<tr>
<th>Consult</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EER</td>
<td>Complete</td>
<td>Acceptable recommended by the Office of Compliance on 10/19/98</td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Pending</td>
<td>Will be submitted after the deficiencies have been addressed by the applicant</td>
</tr>
<tr>
<td>Trademark</td>
<td>Pending</td>
<td>Submitted on 1/7/97</td>
</tr>
<tr>
<td>Statistics</td>
<td>Pending</td>
<td>Submitted on 9/10/98</td>
</tr>
<tr>
<td>Pharma/Tox</td>
<td>Pending</td>
<td>Submitted on 9/21/98</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Pending</td>
<td>Submitted on 8/18/98</td>
</tr>
<tr>
<td>Environmental Assessment</td>
<td>Categorical exclusion</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>

REMARK/COMMENTS:
Drug Substance: There are a number of deficiencies related to the drug substance. The deficiencies are conveyed to the applicant and they should be addressed before this NDA can be approved.

Drug Product: There are quite a few deficiencies related to drug product section. They need to be addressed before approval is recommended.

CONCLUSIONS AND RECOMMENDATIONS:
This NDA cannot be approved until all the CMC deficiencies are satisfactorily addressed and pending consults are completed.

/\s/ 11/30/95
Xiao Hong Chen, Ph.D., Review Chemist

/\s/ 11/30/95
Nallaperumal Chidambaram, Ph.D.
Review Chemist
CC:
Orig. NDA 20-954
HFD-150 Division File
HFD-150/XChen
HFD-150/NChidambaram
HFD-150/LZhou
HFD-150/PGuinn
HFD-810/Directors