PROJECT MANAGER REVIEW OF LABELING - AMENDED

NDA: 20-954 / SLR-003 **Drug:** Busulfex™ (busulfan) Injection

Submission Date: June 19, 2000 **Applicant:** Orphan Medical, Inc. (OMI)

Receipt Date: June 20, 2000 **Review Completed:** April 23, 2002

This review amends the original Project Manager Labeling Review that was signed in DFS on April 10, 2002. Specifically, the sections that are amended are Item 8.b.(ii) under the "REVIEW" section (page 10) and the "RECOMMENDED REGULATORY ACTION" section (page 13).

After an April 23, 2002 discussion between the chemistry reviewer (N. Chidambaram, Ph.D.) and the medical team leader (D. Griebel, M.D.), they decided there was no clinical or safety concerns that would justify the inclusion of the "—" before the phrase "0.5 mg/mL" in the second sentence of the Preparation for Intravenous Administration subsection of the DOSAGE AND ADMINISTRATION section.

RECOMMENDED REGULATORY ACTION:

The action letter will be modified and the supplement approved without any modifications.

See appended electronic signature page for official signatures of those listed below.

/S/

Dianne Spillman /date
Regulatory Project Manager

/S/

Donna Griebel, M.D. /date
Medical Team Leader

/S/

Dotti Pease /date
Chief, Project Management Staff

Draft by: dds\4-23-02

☑ Checked in DFS 4-5-02... NDA 20-954/SLR-003
cc: D.Pease/N.Chidambaram/R.Dagher
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/s/

Dianne Spillman
4/23/02 03:09:13 PM
CSO

Donna Griebel
4/23/02 05:31:56 PM
MEDICAL OFFICER

Dotti Pease
4/24/02 09:28:51 AM
CSO

PROJECT MANAGER REVIEW OF LABELING

NDA: 20-954 / SLR-003 **Drug:** Busulfex™ (busulfan) Injection

Submission Date: June 19, 2000 **Applicant:** Orphan Medical, Inc. (OMI)

Receipt Date: June 20, 2000 **Review Completed:** January 4, 2002

BACKGROUND:

This labeling supplement contains Final Printed Labeling (FPL) of the package insert with major revisions to the DOSAGE AND ADMINISTRATION section. The rationale for these changes are described in Attachment 1of the June 19, 2000 submission.

Upon further review, there were also changes to the CLINICAL PHARMACOLOGY, CLINICAL STUDIES, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE, HOW SUPPLIED and HANDLING AND DISPOSAL sections. Although most of these changes are minor and appear editorial in nature, the clinical and chemistry reviewers should still evaluate those changes identified by the project manager in the DISCIPLINE-SPECIFIC INFORMATION section of this labeling review.

Following is a list of relevant documents:

February 4, 1999	**FDA**	**Approval Letter** for Busulfex, NDA 20-954 (see NDA archival volume A1.1B).
February 11, 1999	**OMI**	**Final Printed Labeling (FPL)** submitted (COMIS code: FA. See NDA archival volume A12.1).
August 10, 1999	**FDA**	**Letter** indicating submitted FPL is unacceptable (see NDA archival volume A12.1).
September 2, 1999	**OMI**	**Letter** responding to August 10, 1999 FDA letter (see NDA archival volume A14.1).
June 19, 2000	**OMI**	**Supplement 003** submitted as Changes Being Effected labeling supplement (COMIS code: SLR-003).

Unless specified otherwise, throughout this review the applicant's deletions are underlined, and their modifications and/or additions are **bolded**.

DISCIPLINE-SPECIFIC INFORMATION:

In this document, the project manager requests that the clinical and CMC reviewers evaluate the applicant's package insert revisions. If the reviewers agree with the changes and do not recommend any modifications to the applicant's proposed labeling, they should indicate this by signing this review, first in hard copy, then in DFS. If the reviewers concur with some, but not all, of the changes, they should note this when signing the hard copy and the DFS version of this labeling review.

If the chemistry and clinical reviewers recommend modifications to the proposed labeling, they should write up a separate review documenting these changes. In order to expedite the discipline-specific review of this document, the clinical and CMC reviewers should take note of the following:

CLINICAL:
- Items 4a, 5a, 5b, 6b(ii), 6b(iii), 6c(iv), 6e, 6f, 6g, 6h(i), and 8a(iii) in the REVIEW section of this document requires clinical review by Ramzi Dagher, M.D.
- Dr. Dagher should sign the last page of this review if he concurs with the changes. Otherwise, he should write a separate review indicating the changes that should be relayed to OMI.

CMC:
- Items 8b(ii), 8b(iii), 9, 11a, 11c and 12 in the REVIEW section of this document requires chemistry review by N. Chidambaram, Ph.D.
- Dr. Chidambaram should sign the last page of this review if he concurs with the changes. Otherwise, he should write a separate review indicating the changes that should be relayed to OMI.

DOCUMENTS REVIEWED:

Since the February 11, 2001 FPL was deemed unacceptable on August 10, 1999, I compared the proposed package insert submitted in this supplement (SLR-003) with the package insert that accompanied the February 4, 1999 approval letter for the original NDA submission.

REVIEW:

1. Throughout the package insert, when the established name "(busulfan)" follows the proprietary name Busulfex, the registered "®" symbol now replaces the trademark symbol "™".

   These changes are acceptable, are editorial in nature, and do not require review by any discipline.

2. In the **CLINICAL PHARMACOLOGY** section, there are two editorial changes.

   a. In the first sentence, a hyphen ("-") was inserted between the words "four" and "carbon".

   b. In the heading for Table 1, the "n" in the phrase "...n=59)" is now capitalized and appears as "...N=59)".

   Both of these changes are acceptable, are editorial in nature, and do not require review by any discipline.

3. In the **CLINICAL STUDIES** section, there were two changes, both of which occurred in Table 2.

   a. The heading for Table 2 is now in bold font.

   b. In the seventh row of the table, in the first column under the information for "Devergie, 1995", the abbreviation "Bu" was changed to uppercase letters and now appears as "BU".

   Both of these changes are acceptable, are editorial in nature, and do not require review by any discipline.

4. In the **WARNINGS** section, there were three changes, only the first of which requires review by the clinical reviewer.

   a. In the **Hepatic** subsection, the abbreviation "VOD" appears four times. In each instance, OMI changed the abbreviation to "HVOD".

      The clinical reviewer should review this change, and if acceptable, should indicate his concurrence by signing this review.

   b. In the **Cardiac** subsection, the established name now follows the proprietary name BUSULFEX. The last sentence in this section now reads:

      "No patients treated in the BUSULFEX **(busulfex) Injection** clinical trials experienced cardiac tamponade."

      This change complies with item 3 of the Division's August 10, 1999 letter, is acceptable, editorial in nature, and does not require review by any discipline.

   c. In the last paragraph, second sentence, of the **Carcinogenicity, Mutagenicity, Impairment of Fertility** subsection, OMI corrected the word "spermatogenisis" to "spermatogenesis".

This change is acceptable, is editorial in nature, and does not require review by any discipline.

5. In the **PRECAUTIONS** section, there were four editorial changes. The first two of require review by the clinical reviewer.

   a. In the **Laboratory Tests** subsection, the end of the second paragraph was changed

      from: "...and bilirubin should be evaluated daily through transplant day 28."

      to: "...and bilirubin should be evaluated daily through **BMT** day **+**28."

   Although this change appears editorial in nature, the clinical reviewer should review this change, and if acceptable, he should indicate his concurrence by signing this review.

   b. In the first paragraph of the **Drug Interactions** subsection, the first sentence was changed

      from: "Itraconazole decreases busulfan clearance by up to 25%, and may produce AUCs > 1500 μM•min in some patients."

      to: "Itraconazole decreases busulfan clearance by up to 25%, and may produce **an** AUC > 1500 μM•min in some patients."

   Although this change appears editorial in nature, the clinical reviewer should review this change, and if acceptable, he should indicate his concurrence by signing this review.

   c. In the **Pregnancy** subsection, the word "WARNINGS" is now in **bold** font.

   This change is acceptable, is editorial in nature, and does not require review by any discipline.

   d. In the **Other** subsection, the word "the" was added before the word "interpretation". The sentence now reads:

      "This cytologic dysplasia may be severe enough to cause difficulty in **the** interpretation of exfoliative cytologic examinations of the lungs, bladder, breast and the uterine cervix."

   This change is acceptable, is editorial in nature, and does not require review by any discipline.

6. In the **ADVERSE REACTIONS** section, OMI made numerous changes. Specifically, the changes were:

   a. In the second sentence of the first paragraph, the comma was moved after the word "trial". The sentence was changed

      from: "In a Phase 1, trial the maximum tolerated dose (MTD)..."

      to: "In Phase 1 trial, the maximum tolerated dose (MTD)..."

      This change is acceptable, is editorial in nature, and does not require review by any discipline.

   b. In the **BUSULFEX Clinical Trials** subsection, there were three changes, the last two of which requires clinical review.

      (i) In the first sentence, the established name now follows the proprietary name BUSULFEX.

      This change complies with item 3 of the Division's August 10, 1999 letter, is acceptable, editorial in nature, and does not require review by any discipline.

      (ii) The first part of the second sentence was changed

      from: "Ninety three percent (93%) of evaluable patients receiving this dose of BUSULFEX maintained AUCs less than 1,500 μM•min for dose 9,..."

      to: "Ninety-three percent (93%) of evaluable patients receiving this dose of BUSULFEX maintained **an** AUC less than 1,500 μM•min for dose 9,..."

      Although this change appears editorial in nature, the clinical reviewer should review this change, and if acceptable, he should indicate his concurrence by signing this review.

      (iii) The last part of the second sentence was changed

      from: "...which has generally been considered the level that minimizes the risk of VOD."

      to: "...which has generally been considered the level that minimizes the risk of **H**VOD."

Although this change appears editorial in nature, the clinical reviewer should review this change, and if acceptable, he should indicate his concurrence by signing this review.

c. In **Table 4**, there were four changes, of which only the last one requires clinical review.

(i) The heading for Table 4 was changed to Table **3**.

This change is appropriate since there was no Table 3 in the original approval. The change is acceptable, editorial in nature, and does not require review by any discipline.

(ii) Under the CARDIOVASCULAR SYSTEM row, the "Hypertension" entry now precedes the "Thrombosis" entry. The row was changed

from:

CARDIOVASCULAR SYSTEM	
Tachycardia	44
Thrombosis	33
Hypertension	36
Vasodilation	25

to:

CARDIOVASCULAR SYSTEM	
Tachycardia	44
Hypertension	**36**
Thrombosis	**33**
Vasodilation	25

(iii) Under the METABLIC AND NUTRITIONAL SYSTEM row, the "Hyperglycemia" entry now precedes the "Hypokalemia" entry. The row was changed

from:

METABOLIC AND NUTRITIONAL SYSTEM	
Hypomagnesemia	77
Hypokalemia	64
Hyperglycemia	66
Hypocalcemia	49
Hyperbilirubinemia	49
Edema	36
SGPT Elevation	31
Creatinine Increased	21

to:

METABOLIC AND NUTRITIONAL SYSTEM	
Hypomagnesemia	77
Hyperglycemia	**66**
Hypokalemia	**64**
Hypocalcemia	49
Hyperbilirubinemia	49
Edema	36
SGPT Elevation	31
Creatinine Increased	21

In the changes outlined in item (ii) and (iii) above, the applicant now lists the events according to decreasing percent incidence. These changes are acceptable, editorial in nature, and do not require review by any discipline.

(iv) The notation at the end of the table was changed

from: "All reported adverse events regardless of severity (toxicity grades 1-4)"

to: "**Includes a**ll reported adverse events regardless of severity (toxicity grades 1-4)"

Although this change appears editorial in nature, the clinical reviewer should review this change, and if acceptable, he should indicate his concurrence by signing this review.

d. In the second sentence of the **Hematologic** subsection, the spelling of "administered" was corrected from "adminstered".

This change is acceptable, is editorial in nature, and does not require review by any discipline.

e. In the **Gastrointestinal** subsection, there were two changes in the third sentence. The third occurrence in the word "in" was deleted and a plus sign "+" was added after the word "Day". The sentence was changed

from: "Mild or moderate nausea occurred in 92% of patients in the allogeneic clinical trial, and mild or moderate vomiting in occurred in 95% through BMT day 28; nausea was severe in 7%."

to: "Mild or moderate nausea occurred in 92% of patients in the allogeneic clinical trial, and mild or moderate vomiting occurred in 95% through BMT day +28; nausea was severe in 7%."

Although this change appears editorial in nature, the clinical reviewer should review this change, and if acceptable, he should indicate his concurrence by signing this review.

f. In the **Hepatic** subsection, the third sentence was changed by the addition of the word "hepatic" before the phrase "veno-occlusive disease". The sentence now reads:

> "Hyperbilirubinemia was associated with graft-versus-host disease in six patients and with **hepatic** veno-occlusive disease in 5 patients."

The clinical reviewer should review this change, and if acceptable, should indicate his concurrence by signing this review.

g. In the **Hepatic veno-occlusive disease** subsection, the abbreviation "VOD" appears two times, once in each of the two sentences. In each instance, OMI changed the abbreviation to "**H**VOD".

The clinical reviewer should review this change, and if acceptable, should indicate his concurrence by signing this review.

h. In the **Neurologic** subsection, there were two changes, only the first requires clinical review.

(i) In the third sentence, the abbreviation "VOD" was changed to "**H**VOD".

The clinical reviewer should review this change, and if acceptable, should indicate his concurrence by signing this review.

(ii) In the sixth sentence, the established name now follows the proprietary name BUSULFEX.

This change complies with item 3 of the Division's August 10, 1999 letter, is acceptable, editorial in nature, and does not require review by any discipline.

i. In the second sentence of the **Oral Busulfan Literature Review** subsection, the phrase "Table 5" was changed to "Table **4**".

This change is acceptable, editorial in nature, and does not require review by any discipline.

j. In Table 5, the heading was changed to "Table **4**" and the entire heading is in **bold** font.

These changes are acceptable, editorial in nature, and do not require review by any discipline.

7. In the third sentence of the **OVERDOSAGE** section, a comma was added after the phrase"...hypoplasia/aplasia and pancytopenia...." The sentence now reads:

   "The principal toxic effect is profound bone marrow hypoplasia/aplasia and pancytopenia, but the central nervous system, liver, lungs, and gastrointestinal tract may be affected."

   This change is acceptable, is editorial in nature, and does not require review by any discipline.

8. In the **DOSAGE AND ADMINISTRATION** section, OMI made several changes.

   a. Three of the changes are in the second paragraph. Only the last requires clinical review.

      (i) In the second sentence, the established name now follows the proprietary name BUSULFEX.

      This change complies with item 3 of the Division's August 10, 1999 letter, is acceptable, editorial in nature, and does not require review by any discipline.

      (ii) In the fifth sentence, a comma was changed to a semicolon. The phrase "...IBW ($kg_{\perp}$ women) = 45 + 0.91x ..." now reads

      "...IBW (kg; women) = 45 + 0.91x...."

      This change is acceptable, is editorial in nature, and does not require review by any discipline.

      (iii) The phrase "in combination with BUSULFEX" was deleted from the last sentence. The sentence was changed

      from: "Cyclophosphamide <u>in combination with BUSULFEX</u> is given on each of two days as a one-hour infusion at a dose of 60 mg/kg beginning on BMT day –3, six hours following the 16th dose of BUSULFEX."

      to: "Cyclophosphamide is given on each of two days as a one-hour infusion at a dose of 60 mg/kg beginning on BMT day –3, six hours following the 16th dose of BUSULFEX."

The medical reviewer should review this change, and if acceptable, should indicate his concurrence by signing this review.

b. In the **Preparation for Intravenous Administration** subsection, there were several changes.

(i) Throughout this section, the phrase "D5W" appears four times. In each instance, OMI changed the "5" in "D5W" to a subscript so that in this FPL it appears as "D_5W".

This change is acceptable, is editorial in nature, and does not require review by any discipline.

(ii) The second sentence was changed

from: "The diluent quantity should be 10 times the volume of BUSULFEX, ensuring that the final concentration of busulfan is approximately ≥ 0.5 mg/mL."

to: [redacted]

The justification for this change is provided in ATTACHMENT 1 of the June 19, 2000 submission. The chemistry reviewer should review this change for acceptability.

On March 28, 2002, the chemistry reviewer noted that the above changes are not acceptable and that OMI should revert to the original wording at the next printing. This change can be submitted in the next annual report. If the chemistry reviewer finds this acceptable, he should indicate his concurrence by signing this review.

(iii) At the end of the second paragraph of this section, two sentences were added as follows:

"USE OF FILTERS OTHER THAN THE SPECIFIC TYPE INCLUDED IN THIS PACKAGE WITH EACH AMPOULE IS NOT RECOMMENDED. DO NOT USE POLYCARBONATE SYRINGES WITH BUSULFEX."

The first sentence was moved from the **HOW SUPPLIED** section because OMI stated "it was more applicable to the preparation of intravenous infusions." This change appears appropriate and editorial in nature; however, the chemistry reviewer should review this change, and if acceptable, should indicate his concurrence by signing this review.

The second sentence is new. The justification for this change is provided in ATTACHMENT 1 of the June 19, 2000 submission. The chemistry reviewer should review this change, and if acceptable, should indicate his concurrence by signing this review.

9. In the **HOW SUPPLIED** section, the supply information after the NDC number was changed

   from: "10 mL (6mg/mL) in packages of eight ampoules including eight compatible 25 mm 5.0 µm Nylon Membrane syringe filters."

   to: "10 mL (6mg/mL) in packages of eight ampoules including eight compatible 25 mm 5 **micron** Nylon Membrane syringe filters."

   The chemistry reviewer should review this change, and if acceptable, should indicate his concurrence by signing this review.

10. In the **HANDLING AND DISPOSAL** section, the phrase "Rx only" was deleted.

    This phrase was redundant in this section as it is already in the TITLE section of the labeling. This change is acceptable, is editorial in nature, and does not require review by any discipline.

11. In the general information immediately following the **HANDLING AND DISPOSAL** section, OMI made three changes.

    a. OMI modified the manufacturing information. Specifically, OMI changed the information

       from: "**Manufactured for:**
       Orphan Medical Inc
       Minnetonka, Minnesota 55305

       Manufactured by:
       Ben Venue Laboratories
       Bedford, Ohio 44146"

       to: "**Distributed by:**
       Orphan Medical, Inc.
       Minnetonka, Minnesota 55305"

       This change appears acceptable and editorial in nature, however, the chemistry reviewer should review this change; and if acceptable, should indicate his concurrence by signing this review.

    b. OMI moved the following statements after the **REFERENCES** section.

       "For questions of a medical nature call 1-888-867-7426 (1-888-8ORPHAN).

To order BUSULFEX call 1-800-359-4304."

This change is acceptable, is editorial in nature, and does not require review by any discipline.

c. The following statements are now included

"United States Patent numbers 5,430,057 and 5,559,148. Patents pending in Canada and European Union.

In the Division's August 10, 1999 letter, the Division instructed OMI to delete the patent information from the February 11, 1999 FPL because according to 21 CFR 201.56(b), "The labeling shall be informative and accurate and neither promotional in tone nor false or misleading in any particular". OMI temporarily addressed this concern with stickers. However, in OMI's September 2, 1999 submission, OMI justifies the inclusion of a patent statement by citing that under Title 35 of the United States Code, "a patent notice must be included on either the product or product package to provide sufficient patent notice to the public." According to OMI, since the patent statements do not mention a drug indication, they are not in violation of 21 CFR 201.56(b).

Although this change appears editorial in nature, the chemistry reviewer should review this change, and if acceptable, he should indicate his concurrence by signing this review.

d. OMI changed the revision information

from: "Rev. 12/98"

to: **"Revision Date: February 2000"**

This change is acceptable, is editorial in nature, and does not require review by any discipline.

12. In the Division's August 10, 1999 letter, the FPL was deemed unacceptable for several reasons. We requested that the name Busulfex as it is printed in the labeling text and labeling packages be changed so that the "B" is the same size font as "usulfex" and is no more than two times larger than "(busulfan) Injection". In addition, the vertical and horizontal lines going through the name Busulfex should be deleted. OMI responded to our concerns in a letter dated September 2, 1999.

In the package insert FPL submitted for this supplement, the proprietary name, along with the established name, appears as a "logo" three times. The September 2, 1999 correspondence appears to provide justification for retaining this "logo" in

the labeling packages; however, none of the examples OMI provided presented the "logo" in the package insert/labeling text.

Retaining the "logo" in the package insert does not appear to this project manager to be in violation of the regulations. However, the chemistry reviewer should determine whether OMI's September 2, 1999 response and justification are adequate, and if acceptable, should indicate his concurrence by signing this review.

RECOMMENDED REGULATORY ACTION:

The chemistry and clinical reviewers should review the changes specific to their discipline. If the reviewers concur with the changes and do not recommend any modifications to the labeling, they should indicate this by concurring with this review, first in hard copy then in DFS. The project manager will then issue an approval letter for this supplement.

If the reviewers concur with some of the changes, but not all of the changes, they should note this when signing the hard copy and the DFS version of this labeling review. If the chemistry and clinical reviewers recommend modifications to the proposed labeling, they should write up a separate review documenting these changes. (Note: after discussion with the chemistry reviewer on March 28, 2002, I agreed to incorporate his recommendation regarding item 8.b.(ii) as part of this review – see comment below).

The following chemistry recommendation will be relayed in the approval letter.

"However, please note the following minor editorial revision listed below. This change should be made at the next printing or within six months, whichever comes first, and noted in the next annual report.

You should [redacted]

to: "The diluent quantity should be 10 times the volume of BUSULFEX, so that the final concentration of busulfan is approximately $\geq$ 0.5 mg/mL."

The inclusion of the greater than or equal to sign will ensure the concentration of busulfan is not less than 0.5 mg/mL."

See appended electronic signature page for official signatures of those listed below.

draft: /s/ 1-4-02
Dianne Spillman /date
Regulatory Project Manager

draft: /s/ 4-2-02
N. Chidambaram, Ph.D. /date
Chemistry Reviewer

draft: /s/ 1-8-02
Dotti Pease /date
Chief, Project Management Staff

draft: /s/ 4-2-02
Ramzi Dagher, M.D. /date
Medical Reviewer

Draft by: dds\1-3-02
Edited by: dds\1-4-02\4-2-02\4-4-02

☑ Checked in DFS 4-5-02... NDA 20-954/SLR-003
cc: D.Pease/N.Chidambaram/R.Dagher
HF-2/Medwatch
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/s/

Dianne Spillman
4/5/02 11:42:43 AM
CSO

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Nallaperumal Chidambaram
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CHEMIST

Ramzi Dagher
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MEDICAL OFFICER