CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)
20-954/S-001

Trade Name: Busulfex

Generic Name(s): (busulfan)

Sponsor: Orphan Medical, Inc.

Agent:

Approval Date: December 23, 2002

Indication: Provides for changes in the WARNINGS Hepatic subsection

NDA : 20954/SLR-001

Drug : Busulfex Injection

Applicant : Orphan Medical, Inc.

Medical Officer : Ramzi Dagher, M.D.

The project manager has completed a review of this labeling supplement. The medical officer concurs with the proposed changes except as outlined below for specific items :

Item #2 – VOD was verified in the following 5 patients enrolled in OMC-BUS-4 ;01-404, 01-416, 02-403, 05-401, and 06-405. Therefore, the proposed change in the number of patients with verified VOD from 5 to 3 is unacceptable. The mortality rate from VOD for the overall study population (2/61 = 3%) can be presented, but the fatality rate in patients with VOD (2/5 = 40%) should also presented. The sentence could be revised to the following : " Hepatic veno-occlusive disease developed in 8% (5/61) patients treated with Busulfex in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from VOD in the entire study population of 2/61 (3%).

Item 4e – See item #2 above

Item 4f – For clarification, the term 'weight increase (8%)' should be modified to 'documented weight increase (8%)'. Because it is unclear what additional information is provided by listing the hypervolemia percentage in addition to edema, the percentage of hypervolemia should not be included.

Item 4h – i) Alveolar hemorrhage was documented in 3 patients (01-412, 02-403, and 05-401). Therefore, the proposed change in the number from 3 to 2 is unacceptable.

ii) All 3 patients required ventilatory support and died, therefore the proposed change is unacceptable.

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/s/

Ramzi Dagher
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MEDICAL OFFICER

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Received 9 February 1987.
Accepted 26 March 1987.

0041-1337/87/4406-0778$02.00/0
TRANSPLANTATION

Vol. 44, No. 6
Printed in U.S.A.

VENOOCCLUSIVE DISEASE OF THE LIVER FOLLOWING BONE MARROW TRANSPLANTATION[1]

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Review of 235 consecutive patients undergoing bone marrow transplantation was performed in order to define the clinical syndrome of venoocclusive disease of the liver (VOD) in these patients. Analysis of all patients with histologically proven VOD revealed a consistent clinical syndrome of liver dysfunction occurring within the first 3 weeks after marrow infusion. This was characterized by hyperbilirubinemia peaking at greater than or equal to 2 mg/dl with at least 2 of 3 other findings: hepatomegaly, ascites, and 5% or greater weight gain. VOD developed in 22% (52 of 235). A persistently elevated aspartate aminotransferase (SGOT) prior to transplant was associated with an increased risk of developing VOD by multivariate analysis (P=0.0003), and acute leukemia in first remission was associated with a decreased risk (P=0.02). Neither the preparative regimen (busulfan and cyclophosphamide versus cyclophosphamide and total body irradiation) nor the type of graft (allogeneic versus autologous) influenced the occurrence. Twenty-four of these 52 patients (47%) died with VOD (10% of the entire group). This makes VOD the third leading cause of death in our allogeneic graft recipients, and the second leading cause in our patients receiving autologous transplants. VOD is a common complication of bone marrow transplantation and has a specific clinical presentation, which usually allows diagnosis without the need of liver biopsy.

Venoocclusive disease of the liver (VOD)* is characterized by hepatomegaly and ascites and is similar clinically to the Budd-Chiari syndrome. However, VOD results from fibrous narrowing of small hepatic venules and sinusoids rather than occlusion of the main hepatic veins. Although VOD was initially described after the ingestion of bush tea containing pyrrolizidine alkaloids (*1–4*), it has since been associated with multiple clinical settings. These include hepatic irradiation (*5–7*), and the administration of various chemotherapeutic agents (*8–14*). In 1979, VOD following bone marrow transplantation was first reported (*15*), and it is now recognized as a common complication of the pretransplant preparative regimen. Various preparative regimens containing combination as well as single-agent chemoradiation therapy have been implicated (*16–22*).

McDonald and coworkers, in an analysis of 255 consecutive patients undergoing bone marrow transplantation after preparation predominantly with cyclophosphamide and total body irradiation, found a frequency of VOD of 21%, with 45% of these patients dying with progressive liver disease (*23, 24*). They also found that an elevated SGOT prior to beginning the marrow transplant preparative regimen was a positive risk factor for the development of VOD, while age less than 15 years

[1] This work was supported in part by CA 15396 and 2 T32 CA 0907-06 from the National Cancer Institute.

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* Abbreviations used: GVHD, graft-versus-host disease; SGOT, aspartate aminotransferase; VOD, venoocclusive disease of the liver.

and a diagnosis of acute lymphocytic leukemia were negative risk factors.

We have retrospectively reviewed 235 consecutive patients undergoing bone marrow transplantation in order to establish the clinical characteristics of VOD in our patients, and to identify factors that may be related to its development and outcome. Since we have a large experience with 2 different marrow transplant preparative regimens (cyclophosphamide with total body irradiation and busulfan with cyclophosphamide), we also wanted to compare the features of VOD in these 2 regimens.

MATERIALS AND METHODS

Patient selection and diagnostic criteria. Between January 1, 1982 and March 31, 1985, 235 patients underwent bone marrow transplantation at the Johns Hopkins Oncology Center. Of the 158 of these patients who have died, autopsies have been performed on 57. Liver biopsy was performed on another 6 patients who did not have an autopsy. Twelve of the autopsies could not be used because there was no liver material in 7 and there were inadequate specimens for diagnosis in 5. Liver biopsy material was inadequate to make a specific diagnosis in 3 patients. Therefore, liver histology was evaluable in 48 patients. One of the authors (Beschorner WE) blindly reviewed all the liver histology. VOD was said to be present if at least 1 of 2 basic patterns was seen, and the histologic changes were further described as mild, moderate, or severe. In 1 pattern, fibrosis is restricted to the central veins. In the second pattern, there is increased fibrosis in the sinusoids of the centrilobular region. Masson trichrome stains were performed on sections in order to better visualize the fibrosis.

The central venous pattern of VOD is recognized by increased fibrosis under the endothelium and in some cases by increased fibrosis in the adventitial region. The changes are most prominent in the small and medium central veins. The changes were classified mild in any cases with subendothelial fibrosis, moderate with 50% or greater occlusion of the lumen in many of the veins, and severe with 80–100% occlusion of the lumen. The cases with moderate to severe central vein changes usually had associated centrilobular congestion and widening of the centrilobular sinusoids.

The sinusoidal pattern of VOD is characterized by increased fibrosis in the centrilobular sinusoids, usually without significant changes to the central veins (*17*). The mild cases of sinusoidal VOD were those with fibrosis that was detectable only with the Masson stain. There was rarely any alteration seen in the centrilobular hepatocytes. The moderate cases had sinusoidal fibrosis that was readily recognized with the hematoxylin and eosin stains, extended well into the lobule, and was associated with some disruption of the plates of centrilobular hepatocytes. Cellular debris was usually evident in the sinusoids as well. Severe sinusoidal VOD had marked fibrosis with near obliteration of the centrilobular region and marked disruption of the centrilobular plates. The remaining centrilobular hepatocytes were often necrotic or had nuclear atypia. The moderate and severe cases of sinusoidal VOD usually had associated centrilobular congestion.

Twenty-one patients had histologic evidence of VOD of the liver. Only 1 of these 21 patients had no clinical evidence of liver dysfunction. Review of the other 20 patients revealed that each developed a distinctive clinical syndrome marked by the development of liver dysfunction by day 21 after bone marrow infusion. The liver dysfunction was characterized by hyperbilirubinemia, which peaked at greater than or equal to 2 mg/dl, and at least 2 of 3 other findings: hepatomegaly, which was usually painful, ascites, and 5% or greater weight gain. Using these criteria for the clinical diagnosis of VOD, we retrospectively reviewed the charts of the above 235 consecutive bone marrow transplant patients and classified them as either having or not having clinical VOD. A patient was given the diagnosis of VOD if the clinical criteria for the diagnosis was present or if histologic material revealed the diagnosis. Any differences between the histologic and clinical diagnosis of VOD were settled in favor of the histology.

Clinical variables analyzed. The pretransplant characteristics listed in Table 1 were analyzed for their effect on the development of VOD. The category of "others" listed under "diagnosis" includes 17 patients with non-Hodgkin's lymphoma, 4 with metastatic breast carcinoma, 2 with Hodgkin's disease, 2 with rhabdomyosarcoma, and 1 patient each with adrenal leukodystrophy and metachromatic leukodystrophy. Busulfan at 4 mg/kg/day for 4 consecutive days followed by cyclophosphamide at 50 mg/kg/day for 4 days was the preparative regimen used in 82 patients. This includes 66 patients with acute myelocytic leukemia, 6 patients with chronic myelocytic leukemia, 4 patients with breast carcinoma, 3 patients with acute lymphocytic leukemia in third remission, the 2 patients with leukodystrophy, and 1 patient with Hodgkin's disease. Cyclophosphamide at 50 mg/kg/day for 4 consecutive days followed by total body irradiation at 300 R/day for 4 days (or 180 R twice a day for 4 days in 6 patients with non-Hodgkin's lymphoma) was used in all other patients, with the exception of 14 with aplastic

TABLE 1. Frequency of venoocclusive disease by pretransplant characteristics

Characteristic	Frequency (%)	*P* value
Age:		
0–9	3/36 (8)	
10–19	13/55 (24)	
20–29	21/76 (29)	0.15
≥30	15/68 (22)	
Sex:		
Male	26/138 (19)	
Female	26/97 (26)	0.20
Diagnosis:		
Aplastic anemia	3/22 (14)	
Acute lymphocytic leukemia	20/83 (24)	
Acute myelocytic leukemia	18/71 (25)	0.42
Chronic myelocytic leukemia	8/32 (25)	
Others	3/27 (11)	
Preparative regimen:		
Cyclophosphamide Total body irradiation	32/139 (23)	
Busulfan-cyclophosphamide	20/82 (24)	0.95
Type of graft[a]:		
Autologous	13/78 (17)	
Allogeneic	39/154 (25)	0.21
Bilirubin:		
Normal	50/228 (22)	
Elevated	2/7 (29)	0.96
SGOT:		
Elevated	22/46 (48)	
Normal	30/189 (16)	0.000007
Degree of SGOT elevation (IU/L):		
50–100	11/25 (44)	
100–200	8/15 (53)	0.84
>200	3/6 (50)	
Alkaline phosphatase:		
Normal	37/192 (19)	
Elevated	15/43 (35)	0.04
Hepatitis B surface antigen:		
Negative	50/229 (22)	
Positive	2/6 (33)	0.86
Remission/relapse status (acute leukemia):		
Remission	29/122 (24)	
Relapse	9/32 (28)	0.78
Number of remissions or relapses (acute leukemia):		
One	5/43 (12)	
Two or greater	33/111 (30)	0.03

[a] Three patients had syngeneic grafts.

anemia who received just cyclophosphamide with or without cyclosporine as a conditioning regimen. Infusion of bone marrow occurred on day 8 (with cyclophosphamide and total body irradiation) or day 9 (with busulfan and cyclophosphamide) after the start of preparative therapy. Elevations of liver function tests were defined as a bilirubin greater than 1.4 mg/dl, an SGOT greater than 50 IU/dl, and an alkaline phosphatase greater than 125 IU/dl. The other pretransplant categories are self-explanatory. Azotemia was defined as a urea nitrogen greater than 25 mg/dl. Hepatic encephalopathy was diagnosed in patients with neurologic dysfunction in the setting of hepatic failure when either an elevated serum ammonia was present or when no other cause for the neurologic dysfunction could be found. Day 0 was the day of bone marrow infusion, and the day of resolution of VOD was defined as the day the bilirubin improved to 1.4 mg/dl or less.

Platelet transfusion effectiveness was assessed for the 52 patients with VOD and for all patients having histologic material. Corrected posttransfusion increments were calculated at 1 hr and 18–24 hr after transfusion as follows:

$$\frac{(\text{posttransfusion platelet count} - \text{pretransfusion count}) \times \text{body surface area}}{\text{number of platelets transfused } (\times 10^{11})}$$

A patient refractory to platelet transfusions was defined as someone with a 1 hr corrected-platelet-count increment that was persistently less than 7500/mm^3 or with a survival increment at 18–24 hr of persistently less than 4500/mm^3, which could not be corrected with HLA-matched platelets (*25*).

Statistical methods. Univariate analysis by chi-square test was performed on the pretransplant characteristics listed in Table 1 for the risk of developing venoocclusive disease and dying with it once it occurred. Multivariate analysis of the risk of developing disease was performed by multiple stepwise logistic regression to adjust for differences in pretransplant characteristics using maximum likelihood ratio chi-square to determine the levels of significance (*26*). Clinical and laboratory features of VOD were compared by Wilcoxon rank-sum test for day of onset, Student's *t* test for peak laboratory values, and chi-square test for frequency to determine if any features predicted for outcome of VOD. The clinical features were statistically compared between the group of patients with VOD diagnosed by histology and the group diagnosed solely by clinical criteria. To normalize the distribution of laboratory values, logarithmic or reciprocal transformation by the methods of Box and Cox (*27*) were used. Kaplan and Meier survival analysis (*28*) was used to determine the median day of recovery or death from VOD.

RESULTS

Of the 235 consecutive patients undergoing bone marrow transplantation, 52 developed VOD for a frequency of 22%. An estimate of the accuracy of the clinical diagnosis of VOD was made by comparing the results of histology with clinical diagnosis in the 48 patients with adequate liver histology. Twenty of 21 patients (95%) with histologic evidence of VOD were classified as such by clinical criteria, and 25 of 27 (93%) without histologic VOD did not have it on clinical grounds. The 1 patient with VOD histologically, but not by clinical criteria, had no clinical evidence of liver dysfunction at any time following bone marrow transplantation. One patient who appeared to have VOD clinically but not histologically had early onset acute graft-versus-host disease (GVHD) of the liver, and the other had idiopathic cirrhosis.

Table 1 gives the frequency of VOD for the 11 pretransplant characteristics investigated. Univariate analysis shows that a persistently elevated SGOT and a persistently elevated alkaline phosphatase prior to transplant were significantly associated with an increased risk of VOD (P=0.000007 and 0.04, respectively). Being in first remission or first relapse with acute leukemia was associated with a decreased risk (P= 0.03). Age, sex, diagnosis, preparative regimen, type of graft, bilirubin, hepatitis B surface antigen, and remission/relapse status were not associated with an increased risk. However, all 3 cases of VOD seen in aplastic anemia occurred within the group of 7 patients receiving cyclophosphamide and total body irradiation. No cases occurred in the 14 patients with aplastic anemia who received only cyclophosphamide with or without cyclosporine. The statistically significant pretransplant characteristics from the univariate analysis (SGOT, alkaline phosphatase, and the number of remissions or relapses) were further analyzed in a multivariate analysis. In order to utilize a group that would include the category of remission or relapse number, the multivariate analysis was restricted to the 154 patients with acute leukemia. SGOT and remission or relapse number maintained their statistical significance (P=0.0003 and 0.02, respectively) in the multivariate analysis while alkaline phosphatase did not (P= 0.73). Alkaline phosphatase was strongly correlated with SGOT so that the increased occurrence of VOD seen in patients with an elevated alkaline phosphatase could be almost totally explained by the increased occurrence due to a concomitantly elevated SGOT in these patients. Table 1 also shows there was no statistically significant difference in VOD risk based on degree of SGOT elevation.

The frequency of the clinical features associated with VOD are as follows:

Hyperbilirubinemia ≥2 mg/dl	(98%)
Weight gain ≥5%	(92%)
Hepatomegaly	(90%)
Azotemia	(88%)
Elevated alkaline phosphatase	(87%)
Ascites	(85%)
Elevated SGOT	(83%)
Elevated prothrombin time	(52%)
Encephalopathy	(22%)

The onset of weight gain was usually the first sign of disease, occurring on the average 8.6 days after marrow infusion and 2 days before the onset of hyperbilirubinemia. The mean peak weight gain in all 52 patients was 7.6% of baseline. The estimated mean peak value for bilirubin was 13.7 mg/dl with a range of 2–62 mg/dl. Nine patients had a maximum value between 2 and 6 mg/dl; 12 had peak values of 6–10 mg/dl; 12 had peak values of between 10–20 mg/dl, and 18 patients had values that peaked at greater than 20 mg/dl. Hyperbilirubinemia preceded elevations of SGOT and alkaline phosphatase by an average of 2–3 days. The mean estimated peak values for all 52 patients with VOD was 265 IU/L (range 20–7600 IU/L) for SGOT and 294 IU/L (range 100–1860 IU/L) for alkaline phosphatase. The exact onset of hepatomegaly or ascites is difficult to determine since their absolute confirmation often necessitated the results of imaging studies. However, the onset always occurred within 2 weeks of the onset of VOD and usually within 1 week.

Patients whose VOD resolved were compared to those who died with VOD for differences in the frequency of the 11 pretransplant characteristics. These 2 groups were also compared for differences in the days of onset and peak values for hyperbilirubinemia, liver function test elevations, and weight gain. None of the 11 pretransplant characteristics were statistically associated with an increased risk of dying with VOD once it occurred. Only the peak bilirubin value was strongly

related to the outcome of VOD (P=0.00005). There was also a trend toward a relationship between peak SGOT and outcome (P=0.06). The mean peak bilirubin of the patients in whom VOD resolved was 8.1 mg/dl compared to 23.8 mg/dl in those who died with VOD. Only 1 of 19 patients died with VOD when their peak bilirubin was less than 9 mg/dl, and only 1 of 25 patients in whom VOD resolved had a bilirubin that peaked at greater than 15 mg/dl. The outcome of VOD was also strongly related to the development of hepatic encephalopathy (P=0.0005). All 11 patients who developed hepatic encephalopathy died with VOD.

The outcome of the 52 patients with VOD is shown in Table 2. Twenty-five of the patients (48%) had resolution of their disease at a median of 31 days after transplantation or 20 days after onset of VOD. Twenty-four patients (47% of the patients with VOD or 10% of all patients receiving a bone marrow transplant) died with persistent hepatic dysfunction at a mean of 34 days after transplantation or 23 days after onset of VOD. The term "died with VOD" is used rather than "died of VOD" because it is often difficult to ascertain the exact cause of death in many of these patients. This is due to the presence of multiple organ failure including septicemia, azotemia, congestive heart failure, and pulmonary insufficiency. In at least 15 of these patients (29% of patients with VOD disease and 6% of the entire group), hepatic failure apparently was the primary cause of death. In the 9 others who died with persistent VOD, death was multifactorial with liver disease playing a part. There was transient improvement without complete resolution of the hepatic dysfunction in 3 patients with VOD. The liver dysfunction in these patients again worsened, but it did so in the setting of severe acute GVHD. We have used the term "blended into GVHD" to describe the outcome of the VOD in these 3 patients. Recurrent liver dysfunction developed in 8 other patients after resolution of VOD. In no case did this appear to be due to recurrence of VOD. Rather, 7 patients clinically appeared to have hepatic GVHD, and 1 appeared to have non-A, non-B viral hepatitis. In fact, 15 of the 21 autopsies showing VOD also had histologic evidence of GVHD. Ultimately, 36 of the 52 patients with VOD died from all causes within 6 months after transplantation.

The group of patients with VOD by histology and those patients diagnosed only on clinical grounds were compared for differences in the days of onset and peak values for hyperbilirubinemia, liver function test elevations, and weight gain. There was no statistically significant difference in clinical appearance between these 2 groups of patients. There was also no difference in the outcome of VOD between these 2 groups (P=0.65). There was no statistical difference in clinical presentation or outcome between the 2 histologic variants of VOD,

TABLE 2. Outcome in 52 patients with clinical venoocclusive disease

Outcome	N	% of group with venoocclusive disease (n=52)	% of entire group (n=235)	Median day of outcome (range)*
1. Resolved	25	48	11	31 (12–79)
2. Died with venoocclusive disease	24	47	10	34 (11–109)
3. Blended into graft-versus-host disease	3	6	1	–

* Day 0 is the day of marrow infusion.

central venous and sinusoidal. However, only 3 of 10 patients with mild histological VOD died, while 8 of 11 patients with moderate or severe changes died with VOD. There was also no difference in the frequency of histologic variants of VOD based on preparative regimen. There were 7 cases of sinusoidal and 5 cases of central venous VOD associated with cyclophosphamide and total body irradiation, and 5 cases of sinusoidal with 4 cases of central venous disease with busulfan and cyclophosphamide.

Refractoriness to platelet transfusions was seen in 56% (29 of 52) of patients with VOD. Only 36% (9 of 25) of patients whose VOD resolved were refractory compared to 71% (17 of 24) of those who died with VOD. The onset of platelet transfusion failure in these patients was usually within a week of onset of the clinical VOD. Of all patients with evaluable histology who died of any cause, 80% (37 of 48) were refractory to platelet transfusions, including 86% (24 of 28) of those who died with hepatic GVHD.

DISCUSSION

VOD is a common complication of bone marrow transplantation, occurring in 22% of the patients in this series. A review of all the histologically proven cases of VOD in the 235 consecutive patients revealed a consistent clinical syndrome. The disease presented as hepatic dysfunction usually developing by day 21 after marrow transplantation. This was characterized by hyperbilirubinemia, which peaked at greater than 2 mg/dl with at least 2 of 3 other findings: ascites, hepatomegaly, which was usually painful, and weight gain greater than or equal to 5% over baseline.

Although there are many causes of liver disease following bone marrow transplantation, these clinical criteria for VOD define a distinct and specific syndrome that usually allows it to be distinguished from other causes. All the cases of VOD in this series initially presented by day 21 after marrow infusion at a mean of 8.6 days and 10.6 days for first evidence of weight gain and hyperbilirubinemia, respectively. Other causes of liver disease after bone marrow transplantation usually occurred later. For instance, hyperbilirubinemia initially presented at a mean of 22 days (range 13–33) in the 16 patients in this series whose liver histology showed only acute GVHD, the other major cause of liver dysfunction after allogeneic marrow transplants. Ascites, which occurred in 85% of the patients with VOD, was unusual in these 16 patients with acute GVHD of the liver, occurring in only 4 patients. When it did occur, it was generally only after weeks of unrelenting hepatic GVHD. Ascites is also uncommon in other causes of liver dysfunction following marrow transplantation, such as viral or drug-induced hepatitis, parenteral hyperalimentation, and fungal or mycobacterial disease. When it does occur in these diseases, there is usually evidence of severe hepatocellular damage. Although the bilirubin tended to peak at high levels (mean of 13.7 mg/dl) in VOD and correlated with severity as measured by outcome, the SGOT and alkaline phosphatase usually showed only relatively modest peak values (means of 265 IU/L and 294 IU/L, respectively) and were not highly correlated with outcome. The clinical criteria correctly diagnosed 20 of 21 cases (95%) of VOD confirmed histologically and 25 of 27 cases (93%) without disease histologically. Finally, the frequency of VOD (21%) and clinical presentation from the 1 other large series in the literature (*23, 24*) are very similar to this series and underscore the reproducibility of the syndrome.

A persistently elevated SGOT was the most significant pretransplant risk factor for developing VOD (P=0.0003), and it was the only test of liver function independently associated with an increased risk. This was also reported by McDonald and colleagues (*23*). Being in first remission or first relapse with leukemia was associated with a decreased risk (P=0.02). It is likely that an elevated SGOT and advanced remission number both represent markers for underlying liver damage, which could predispose to further liver toxicity occurring from intensive preparative therapy. Although we could not retrospectively define the exact quantity and duration of previous therapy in all patients, the number of remissions should be a rough indication of the amount of previous cytotoxic therapy a patient received. More courses of intensive therapy could lead to increased liver toxicity from the drugs or from viral hepatitis related to transfusions during additional aplasias. McDonald and coworkers also found age less than 15 and a diagnosis of acute lymphocytic leukemia to be associated with a decreased risk, but they did not find a decreased risk for patients with acute leukemia in first remission or relapse. We, however, found no association between age or pretransplant diagnosis and the development of VOD. We also saw no difference in the occurrence rate of VOD for either of our 2 major preparative regimens, cyclophosphamide and total body irradiation or busulfan and cyclophosphamide. There was no statistical difference in the frequency of disease between allogeneic and autologous grafts, showing that GVHD does not play an independent etiologic role in the development of VOD. This also supports the similar findings of the Seattle group (*23*).

Recently, it has been reported that refractoriness to platelet transfusions was seen in 11 of 11 patients developing VOD after bone marrow transplantation, often preceding clinical liver dysfunction (*29*). No etiology for the platelet transfusion failures could be found, however, and 8 of the 11 patients died with VOD. We have found that the 56% incidence of refractoriness to platelet transfusions in our patients with VOD is no different from the 60% incidence seen in all our patients undergoing allogeneic marrow transplantation (unpublished data). Furthermore, only 36% of patients with VOD that resolved were refractory to platelet transfusions, compared to 71% who died with VOD. Also, 80% of autopsied patients who died of any cause were refractory to platelet transfusions, including 86% who died with hepatic GVHD. These data suggest that platelet transfusion refractoriness may be a sign of clinical deterioration after bone marrow transplantation, rather than being specific for VOD.

Centrilobular sinusoidal fibrosis was not included with central vein fibrosis in the histologic description of VOD following marrow transplantation by Shulman and coworkers. It was however, associated with a similar, although possibly milder presentation, and was also considered to be due to chemoradiation toxicity (*19*). We have included sinusoidal fibrosis in the spectrum of histologic VOD for the following reasons. We have found no difference in the presentation or severity of clinical VOD for these 2 histologic patterns. Although an earlier report from this institution suggested that the histologic type of VOD, central venous versus sinusoidal, may differ by preparative regimen (*17*), this was not the case in this series. The reason for this difference may be that the earlier report was strictly an autopsy series and included a number of patients who received 20 mg/kg of busulfan, whereas patients in this series received only 16 mg/kg of busulfan. There also appears to be a strong association between these 2 histological patterns. Centrilobular sinusoidal fibrosis has been reported as part of the histologic description of VOD after pyrrolizidine ingestion (*30*), hepatic irradiation (*6, 7*), and urethane administration (*14*). It may even be the predominant histologic finding in these settings. Furthermore, it has been suggested that radiation and chemotherapy toxicity can injure sinusoidal lining cells as well as central venous endothelium (*6, 14*). Electron microscopic observations in human VOD has revealed extensive damage to both types of cells (*30*). Finally, although sinusoidal fibrosis may not always be specific for the clinical VOD syndrome, it does appear to be specific for this syndrome in the setting of bone marrow transplantation.

Clinical VOD resolved in 10 of the 21 patients who had autopsies. Although these 10 patients died from another unrelated cause (24–166 days after transplantation), they still showed histologic evidence of VOD. There also were no differences in the clinical presentation or outcome of VOD between the patients whose VOD was diagnosed by histology and those diagnosed only by clinical criteria. This suggests that the histologic material on which our clinical criteria for VOD are based represents the full clinical spectrum of VOD, and not just the severest end of the disease spectrum.

VOD is a common complication following bone marrow transplantation. It is the third leading cause of transplantation-related death after GVHD and infections in allogeneic graft recipients, and the second leading cause after infections in patients receiving autologous transplants. Histologic confirmation during life is difficult and may be hazardous. We have seen, as have others (*19*), a number of false-negative liver biopsies, presumably due to sampling error, in patients later proven to have VOD on autopsy. This appears to be particularly a problem with transvenous biopsies. In addition, marrow aplasia causing thrombocytopenia, which is often refractory to platelet transfusions, coagulopathy due to the liver disease, and ascites may be contraindications to the biopsy. We believe that the clinical presentation of VOD is specific and usually diagnostic, obviating the need for histologic confirmation in most cases. Accepting these clinical criteria as diagnostic from a retrospective analysis may be considered premature, and testing these criteria prospectively would obviously be optimal. However, as already mentioned, there are major problems with diagnosing VOD by liver biopsy in these patients, making a prospective study difficult.

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Received 10 February 1987.
Accepted 25 March 1987.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To: Carol Curme	**From:** Sean Bradley
Fax: 952-541-9209	**Fax:** 301-827-4590
Phone: 952-513-6974	**Phone:** 301-594-5750
Pages, including cover sheet: 2	**Date:** October 10, 2002
Re: NDA 20-954/S-001	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your July 26, 2002 submission sent in response to our July 15, 2002 labeling revision for Busulfex (busulfan) Injection, NDA 20954/S001.

Attached is the FDA proposed wording for the labeling for your review. Let us know if you agree with our proposal.

If you have any questions regarding this transmission, please contact me at 301-594-5770.

Sean Bradley, R.Ph.

Regulatory Project Manager

In regards to the wording to be used in the **WARNINGS** section, **Hepatic** subsection, you propose:

"Based on clinical examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 8% (5/61) of patients (3/5 per Jones' criteria) treated with BUSULFEX in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%).

FDA proposal:

"Based on clinical examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 8% (5/61) of patients ~~(3/5 per Jones' criteria)~~ treated with BUSULFEX in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%). Three of the five patients diagnosed with HVOD were retrospectively found to meet the Jones' criteria.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Sean Bradley
Fax:	(952) 541-9209	**Fax:**	(301) 827-4590
Phone:	(952) 513-6974	**Phone:**	(301) 594-5750
Pages (including cover):	4	**Date:**	July 15, 2002
Re:	NDA 20-954 / S-001 – FDA's proposed text		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

Please refer to your supplement S-001, submitted February 16, 1999.

We also refer to your letter/fax date June 7, 2002 sent in response to our May 15, 2002 proposed labeling modifications.

A. Regarding items # 1 and #2, we propose the following wording:

"Based on clinical examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 8% (5/61) of patients treated with BUSULFEX in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%)."

Rationale: We agree with your suggestion for additional wording added to sentence #1 to explain that clinical examination and laboratory findings were used to diagnose HVOD. With regard to the retrospective review using Jones criteria, we suggest removing any reference to this retrospective examination from the package insert since it does not provide any additional information of value. Examination of the two cases in which investigators diagnosed VOD but the cases were not found to meet the Jones criteria for VOD retrospectively shows that indicators of VOD were present, but onset was not noted until after day 21 (Jones criteria require onset before day 21 post BMT)

B. Regarding items #3 and 4, we acknowledge your concurrence with the suggested version.

C. Regarding item # 5,

We do not believe that a change to our previously noted version is justified. In the two cases which you note (01-412 and 05-401), the patients had a diagnosis of DAH at the time of death, and making a distinction that death was not associated with DAH in these cases would be extremely difficult. In any case, the wording FDA has provided does not suggest that DAH was the sole cause of death.

If you agree with our alternate wording and rationale, please provide written documentation of your agreement via fax, followed by a hard-copy submission to the NDA so that we can take action on this supplement.

Regards,

Sean Bradley, R.Ph.

Regulatory Project Manager

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

/s/

Sean Bradley
7/17/02 08:03:59 AM
CSO

ORPHAN MEDICAL

October 16, 2002

Richard Pazdur, M.D.
Division of Oncology Drug Products [HFD-150]
Food and Drug Administration
Center for Drug Evaluation and Research
Woodmont Office Complex II, Room 2055
1451 Rockville Pike
Rockville, MD 20852
(301) 594-2473

Subject: **BUSULFEX® (busulfan) Injection, NDA 20-954/S-001**
Labeling Supplement submitted February 16, 1999
Response to the FDA's facsimile dated October 10, 2002

Dear Dr. Pazdur:

Orphan Medical provides this response to the FDA's facsimile (dated October 10, 2002) in regards to the labeling supplement NDA 20-954/S-001. Reference is also made to the original labeling supplement dated February 16, 1999, FDA correspondences dated May 15, 2002 and July 15, 2002, and Orphan Medical correspondences June 7, 2002 and July 26, 2002.

Orphan Medical concurs with the FDA's proposed wording for the **WARNINGS** section, **Hepatic** subsection of the Busulfex package insert. We request clarification from the FDA that the proposed wording regarding Jones' criteria for HVOD also applies to the **ADVERSE REACTIONS** section, **Hepatic veno-occlusive disease** subsection of the package insert.

If you have any questions or concerns regarding this response, please contact me directly.

Sincerely yours,

Carol S. Curme
Senior Manager of Regulatory Affairs
Phone: 952-513-6974

cc: Dayton T. Reardan, Ph.D., R.A.C., Vice-President of Regulatory Affairs
Sean Bradley, R.Ph., Project Manager

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Orphan Medical, Inc.	October 16, 2002
TELEPHONE NO. *(Include Area Code)* (952) 513-6900	**FACSIMILE (FAX) Number** *(Include Area Code)* (952) 541-9209

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code , telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-954/S-001

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
busulfan (USAN)	Busulfex® (busulfan) Injection

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
sterile liquid	60 mg ampoule	intravenous

(PROPOSED) INDICATION(S) FOR USE: for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☒ Prior Approval (PA)

REASON FOR SUBMISSION Response to the FDA's facsimile, dated October 10, 2002

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

All sites are ready for inspection. SUBSTANCE: Ash Stevens, Inc., 18655 Krause Ave., Riverview, MI, Gary Baker (313-282-3370); PRODUCT: Ben Venue Laboratories, Inc., 300 Northfield Rd., Bedford, OH, Estab. Regis. 1519257, Peter Hansbury (440-232-3320); Metrics, Inc., 1240 Sugg Parkway, Greenville, NC, Estab. Regis. 1062270, Marsha Harrawood (252-752-3800);

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND( ) DMF( ) DMF( ) DMF( ) DMF( ) DMF( ) DMF( ) DMF( ) DMF( ) DMF( ) DMF( ) DMF( ) DMF( )

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j) (2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
X	20.OTHER *(Specify)* Response to the FDA's facsimile, dated October 10, 2002

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Carol S. Curme, J.D., RAC, Senior Manager of RA	10/16/2002

ADDRESS *(Street, City, State, and Zip Code)*	Telephone Number
13911 Ridgedale Drive, Suite 250, Minnetonka, MN 55305	(952) 513-6900

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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Orphan Medical's Response to the FDA's Facsimile dated July 15, 2002

A. Regarding items #1 and #2, the FDA proposed the following wording in the WARNINGS section, Hepatic subsection, and the ADVERSE REACTIONS section, Hepatic veno-occlusive disease subsection:

"Based on clinical examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 8% (5/61) of patients treated with BUSULFEX in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%)."

Orphan Medical's Response:

Orphan Medical concurs with the FDA's proposed language, except for the following revision shown in blue:

"Based on clinical examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 8% (5/61) of patients (3/5 per Jones' criteria) treated with BUSULFEX in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%).

Rationale:

Orphan Medical believes that the package insert should indicate the number of patients who were diagnosed with HVOD per Jones' criteria via the retrospective analysis. Clinical diagnosis of HVOD is controversial and prone to both clinician bias and interference from coexisting illnesses (e.g. GVHD). Jones' criteria were developed to help standardize the diagnosis of HVOD, and the inclusion of this data provides an important means for comparing safety data for Busulfex versus that of other preparative

regimens for transplantation. The requirement of onset within 21 days post BMT can reliably distinguish HVOD from other causes of liver disease with later onset (Jones et al 1987).[1]

B. Regarding items #3 and 4, the FDA acknowledges Orphan Medical's concurrence with the suggested version.

Orphan Medical's Response:

Orphan Medical has incorporated the FDA's versions of items #3 and 4 into the proposed package insert for Busulfex.

C. Regarding item #5, the FDA stated, "We do not believe that a change to our previously noted version is justified . . . ."

Orphan Medical's Response:

Orphan Medical concurs with the FDA's version of Item #5 as written in the Agency's facsimile dated May 15, 2002.

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[1] **Jones RJ, Lee KSK, Beschorner WE, et al. Veno-occlusive disease of the liver following bone marrow transplantation. Transplantation 1987; 44(6): 778-783.**

TABLE OF CONTENTS

SPONSOR NAME:	**Orphan Medical, Inc.**
NDA / SERIAL NUMBER:	**20-954 / S-001**
PRODUCT NAME:	**Busulfex® (busulfan) Injection**
SUBMISSION DATE:	**October 16, 2002**

Form FDA 356h

Cover Letter

FDA Facsimile dated October 10, 2002