Appendix #1  120-Day Safety Update Report Review

The 120-day Safety Update was sent to the Agency on 12/3/98 and received 12/7/98. The report included post-study surveillance data through July 31, 1998. Pertinent references to this report can be found in the NDA Medical Review Document's safety summaries of the pivotal phase 2 studies, OMC-BUS-3 and OMC-BUS-4. There were no new reports of graft failure or unusual toxicity found within the sponsor’s Safety Update. There were 3 additional late deaths related to GVHD reported in the Safety Update of the allogeneic trial, OMC-BUS-4. No new cases of VOD were identified, but there were 3 additional cases of GVHD. This information was included in the NDA Medical Review.

As of the clinical cut-off date for the Safety Update, 39/42 patients treated in OMC-BUS-3 had been observed through BMT Day +100. The median follow-up for the 24 patients who were still disease free at the time of the updated cut-off was 321 days. Fifty of 61 patients on OMC-BUS-4 had been observed through BMT Day +100. The median follow-up for the 38 patients in that study who remained disease free (progression free) at the updated cut-off was 269 days.

A review of the updated number of patients in each study with adverse events reported in the early study time interval – BMT Day –7 to BMT Day +28, revealed that most of the changes were minor and related to the allogeneic study, OMC-BUS-4. Three changes in this early time interval were reported for OMC-BUS-3. The number of patients reporting “Pelvic pain” was increased from one to two (5%), while the number reported having “Pain” decreased by one to 14 (33%). One additional patient was added to the tabulation of those who reported insomnia in this study – 32 (76%). As noted above, 3 additional patients were reported to develop GVHD in the allogeneic study. The remaining adverse events for which additional patients in the allogeneic study were tabulated were all limited to a single additional patient per category: thrombosis, 20 (33%); hypotension, 7 (11%); diarrhea, 51 (84%); prostate increased, 1 (2%); creatinine increased, 13 (21%); dyspnea, 15 (25%); pharyngitis, 11 (18%); skin discoloration, 5 (8%); acne, 4 (7%); ear disorder, 2 (3%). There were no additional reports of seizures, hallucinations, delirium, or confusion in either study. Review of the Safety Update Table of Serious Adverse Events and Deaths for the entire observation period up to the new clinical cut-off date, revealed no unusual events or toxicities that were not discussed at length in the course of the medical review document.

To do a similar comparison of the originally submitted safety data and the Safety Update data regarding the observation period beyond BMT Day +28 is hampered by the sponsor’s pooling of the two studies’ data into one table, Table 9.3.7.20 Summary of 3 and 4 Adverse Events Rated Serious by the Investigator by Body System and COSTART Preferred Term All Patients. However, the only changes in the data from the time interval BMT Day+29 to BMT Day +100 for these events appear limited to an additional SAE “Fever” and a single additional SAE “Interstitial Pneumonitis.”

Labeling reflects the information provided in the Safety Update.
Appendix #2  Methodology Employed by Reviewer in the Conduct of the Literature Review

The sponsor has submitted an analysis of the world literature pertaining to the safety and efficacy of high-dose oral busulfan as conditioning therapy for hematopoietic progenitor cell transplantation. The application describes the methodology of the sponsor’s literature search as beginning with retrieval of 2552 citations for the keywords “busulfan”, “myleran”, “transplant”, “preparative regimen”, and “conditioning regimen”. In a subsequent step, non-MEDLINE reference titles (from EMBASE, BIOSIS, IPA, and Derwent Drug File) were reviewed to eliminate articles that were non-European foreign articles or European articles from minor institutions, articles about post-transplant relapses, articles regarding techniques for measuring engraftment and extracorporeal marrow treatment, and most articles published in a foreign language. After this initial elimination process, 910 non-MEDLINE citations and 698 MEDLINE citations remained.

These 1608 abstracts were reviewed and citations referring to review articles, purging, update or follow-up articles, and articles that focused on detection of post-transplant residual disease were eliminated, leaving 602 articles which were reviewed in completion. That review eliminated 25 additional papers, which were found to be review articles or did not actually pertain to busulfan. The sponsor refers to the remaining 577 papers as the “Overall Database”, and data from these papers regarding patient number and age, disease type, transplant type, cytocitotoxic regimens employed, engraftment, relapse, survival, and toxicities were tabulated.

A “Subset Database” was then defined by two selection criteria. Papers from the “Overall Database” were included in this subset if they included a report of time to engraftment and if the paper reported on ≥ 23 patients. Engraftment had been considered a relevant efficacy measurement. Myeloablation was considered as an alternative efficacy measurement, but none of the “Overall Database” papers reported this information, and since engraftment requires myeloablation, engraftment was felt to be a relevant measure of efficacy. (END of Phase 2 MEETING). When these two selection criteria were applied, the sponsor identified 43 articles for inclusion in the “Subset Database”.

From a review standpoint the following basic issues regarding the quality of the dataset were identified for exploration:

- Were pertinent papers in the “Overall Database” overlooked and not included in the “Subset Database”?
- Were pertinent publications in the world literature not identified and included in the sponsor’s “Overall Database”?
- Was the information abstracted from the 43 articles in the “Subset Database” accurate?
To answer the final question, the reviewer reabstracted the pertinent information from the “Subset Database” articles that had been submitted for review in Volume 1.53 of the application, and compared it to the sponsor’s summary data in Tables.

In an effort to answer the first question, the reviewer inspected Appendix 4, the sponsor’s tabular Summary Information for the 577 Papers Comprising the “overall Database” in Volume 1.52, and identified all papers that were cited as including ≥ 23 patients – 115 publications. Then, using both the tabular Summary Information and the Reference List of the 577 Summarized Articles found in Appendix 3, Volume 1.52 (which included the article titles in the citations), the reviewer devised criteria that would qualify a paper in those 115 publications for audit by the agency to confirm they did qualify for inclusion in the sponsor’s “Subset Database”. Those criteria were as follows:

- Article noted by sponsor to not specify the underlying disease.
- Article noted by sponsor to primarily focus on transplantation in a non-malignant disease setting, e.g., thalassemia.
- Article title indicates the focus is on purging.
- Article title indicated the focus is on second transplant.
- Article title indicated that dimethylbusulfan was the conditioning agent.
- Article title that indicated the focus was a specific toxicity, other than hepatic or pulmonary toxicity.
- Articles that have role of supportive care as main focus, e.g. use of growth factors.
- Articles in a foreign language (1).
- Data provided in Letters

64 citations remained after this process of elimination and the reviewer requested the resulting list of articles below from the sponsor for audit. Fifteen titles (in bold) suggested that the primary focus was toxicity, but these were selected for review to ensure efficacy data had not been overlooked. The italicized citations were provided by the sponsor within the original application and were not included in the article request. Some citations did not clearly correlate between Appendices 3 and 4, and are noted as such below.


Bandini, G, 1994. Toxicity of high-dose busulphan and cyclophosphamide as conditioning therapy for allogeneic bone marrow transplantation in adults with haematological malignancies. (Article included in submission, Volume 1.54)

Bensinger, W.I., 1996. High-dose therapy followed by autologous hematopoietic stem-cell infusion for patients with multiple myeloma.
Blume, K. G., 1993. A prospective randomized comparison of total body irradiation-etoposide vs. busulfan-cyclophosphamide as preparatory regimens for bone marrow transplantation in patients with leukemia who were not in first remission: a SWOG study.


Clift, R.A. 1994. (Tables don’t match – 43 patients with CML and allogeneic transplant)


Copelan, E. A., 1994? (Tables don’t match – 65 patients and autologous transplant)


*Dix, S.P., 1996. Association of busulfan area under the curve with VOD following BMT. Submitted in Volume 54 and 60.*


Hassan, M., 1991? (Tables don’t match – 27 patients)

Huss, R., 1996. Effect of mixed chimerism on GVHD, disease recurrence and survival after HLA-identical marrow transplantation for aplastic anemia or CML.


Klein, J. L., 1996? (Tables don’t match – 89 patients.)


Michel, G., 1997. Late effects of allogeneic bone marrow transplantation for children with acute myeloblastic leukemia in first complete remission: the impact of conditioning regimen without total-body irradiation – a report from the Societe Francaise de Greffe de Moelle. I have this article.

Morgan M., 1991. The toxicity of busulphan and cyclophosphamide as the preparative regimen for bone marrow transplantation.

Nevill, T.J., 1992. Treatment of myelodysplastic syndrome with busulfan-cyclophosphamide conditioning followed by allogeneic BMT.


Petersen, F.B., 1993. Autologous marrow transplantation for patients with AML in untreated first relapse or in second complete remission.


Rapoport, A.P., 1997. Patients greater than or equal to age 40 years undergoing autologous or allogeneic BMT have regimen-related mortality rates and event-free survivals comparable to patients < age 40 years.


Reiffers, J., 1993? (Tables don’t match – 32 patients with CML and autologous BMT)

Reiffers, J., 1994? (Tables don’t match – 95 patients with CML and autologous BMT)


Tutschka, P.J., 1989? (Tables don’t match – 90 patients with leukemia and allogeneic BMT)

Tutschka, P.J., 1991? (Tables don’t match – 123 patients with leukemia and allogeneic BMT)


Vassal, G., 1996? (Tables don’t match – 61 pediatric patients with various malignancies and VOD)


Finally, in an effort to answer the question of whether pertinent publications from the world literature had been omitted from the “Overall Dataset”, the reviewer requested a literature search conducted by the FDA Medical Librarian using the key words “busulfan” and “transplantation”, covering the years 1980-1998. The reviewer also conducted her own MEDLINE search using the following search requests: “busulfan and randomized”, “busulfan and transplant and engraftment”, “busulfan and conditioning regimen”, “busulfan and preparative regimen”, “busulfan and transplantation”. The latter search combination yielded 937 citations. In an effort to narrow the focus of this attempt at verification of the sponsor’s search, the reviewer chose to limit her analysis to review of titles from 1990-1998, and to those citations obtained from the “busulfan and randomized” search. The titles and abstracts were evaluated for potential pertinence to the sponsor’s review, using the same criteria described earlier:

- Article did not appear to specify the underlying disease.
- Article focus is on transplantation in a non-malignant disease setting, e.g., thalassemia.
- Article focus appears to be on purging.
- Article focus is on second transplant.
- Article is on dimethylbusulfan.
- Article focus is on a specific toxicity other than hepatic or pulmonary toxicity.
- Article has supportive care as main focus, e.g. use of growth factors.
Pertinent articles were cross-referenced with Appendices 3 and 4 in Volume 1.52, and if they did not appear were requested for audit. The following 16 articles appeared to have potential relevance after screening using the criteria above, and did not appear in the Volume 1.52 Appendices:


Gondo, H. Bone Marrow Transplant. 1997 November; 20(10): 821. Autologous peripheral blood stem cell transplantation for AML.


Ljungman, P. Bone Marrow Transplant. 1997 December; 20(11): 909. High busulfan concentrations are associated with increased transplant-related mortality in allogeneic bone marrow transplant patients.


Schiller, G. Bone Marrow Transplant. 1998 Jan; 21(2): 141-5. Autologous CD34-selected blood progenitor cell transplants for patients with advanced multiple myeloma.


During the process of auditing the literature review it became apparent that an alternative spelling of busulfan was sometimes used in the world literature. A MEDLINE search was conducted with “busulphan and transplantation” to assess for any additional citations such a spelling change may yield. One hundred fifty-one citations were identified. Using the criteria applied to earlier searches, the reviewer found two additional references to add to the audit for the years 1990-1998:


The 1990-1998 citations from a MEDLINE search using “busulfan and engraftment”, “busulfan and preparative regimen”, and “busulfan and conditioning regimen” were reviewed using the criteria described earlier. The following 7 additional potentially pertinent articles were identified for audit by the reviewer:

Alegre, A. Bone Marrow Transplant. 1998; 21(2): 133. Autologous peripheral blood stem cell transplantation for multiple myeloma: a report of 259 cases from the Spanish Registry.


It should be noted that the sponsor conducted their final literature search on November 2, 1997. Thirteen of the above 25 articles were published before or during October 1997. Two were published in October. Two were published in November 1997. Half of the articles found through the methodology described above were published after the literature search was conducted.

There were 4 additional articles that appeared to meet criteria for audit, but were already included in Appendices 3 and 4. These were also requested, as the abstracted data in Appendix 4 did not appear to correlate with the citation's abstract narrative. They are listed as follows:


The FDA Library conducted an independent literature search at the reviewer's request. The reviewer eliminated articles from that search which were selected for review above, or were part of the sponsor's 43 article "Subset Dataset."

The following articles were obtained for review based on the Library literature search. Those articles with an asterisk were submitted in a literature request to the Library.

SciSearch® Cited Ref Sci:

Storb, R. Bone Marrow Transplantation. 1990; 6(1): 80. HLA-identical marrow transplantation in the leukemias without t-cell depletion.**

Derwent Drug File:


Wingard JR. Blood. 1989; 74(4): 1428. Predictors of Death from Chronic GVHD after bone marrow transplantation.**


BIOSIS Previews:

Schuler, US. Bone Marrow Transplantation. 1998; 22(3): 241. Pharmacokinetics of intravenous busulfan and evaluation of the bioavailability for the oral formulation in conditioning for haematopoietic stem cell transplantation.**

Klein JL. Bone Marrow Transplantation. 1996; 17(4): 479. Bone marrow engraftment following unrelated donor transplantation utilizing busulfan and cyclophosphamide preparatory chemotherapy.**


Van der Jagt, RH. Bone Marrow Transplant. 1991; 8(3): 211. Busulfan and cyclophosphamide as a preparative regimen for bone marrow transplantation in patients with prior chest radiotherapy.**

Hartman, AR. Bone Marrow Transplantation. 1998; 22(5): 439. Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs. total body irradiation: A meta-analysis.**

PubMed:

Appendix #3: Foot Note List of References Associated with the Review


7 Bloomfield DJ. Should Bisphosphonates Be Part of the Standard Therapy of Patients With Multiple Myeloma or Bone Metastases From Other Cancers? An Evidence-Based Review. JCO 16(3), 1998: 1218-1225.


9 Cassileth P. Chemotherapy Compared with Autologous or Allogeneic Bone Marrow Transplantation in the Management of Acute Myeloid Leukemia in First Remission. NEJM 339(23): 1649-1656.


27 Carpenter PA. Allogeneic Bone Marrow Transplantation for Children with Acute Lymphoblastic Leukemia Conditioned with Busulfan, Cyclophosphamide and Melphalan. Bone Marrow Transplantation, 18: 489-494, 1996.


29 Van Besien K. Allogeneic Transplantation for Recurrent or Refractory Non-Hodgkin's Lymphoma with Poor Prognostic Features after Conditioning with Thiotepa, Busulfan, and...


33 Gajewski JL. Bone Marrow Transplants from HLA-Identical Siblings in Advanced Hodgkin’s Disease. JCO, 14(2): 572-578, 1996.


41 Attal M. A Prospective, Randomized Trial of Autologous Bone Marrow Transplantation and Chemotherapy in Multiple Myeloma. NEJM, 335(2):91-96, 1996.


