

Prior Authorization DRUG Guidelines

Alkeran

Effective Date: 10/22/13

Date Developed: 9/3/13 by Albert Reeves MD

Last Approval Date: 1/26/16, 1/24/17, 1/23/18, 1/22/19, 2/18/20

Pharmaceutical Category: Antineoplastic Agent, Alkylating Agent

Authorization Criteria: Palliative treatment of multiple myeloma and non-resectable epithelial ovarian carcinoma

Dosing: Multiple myeloma (palliative treatment):

Note: Response is gradual; may require repeated courses to realize benefit:

Oral: Usual dose (as described in the manufacturer's labeling):

6 mg once daily for 2-3 weeks initially, followed by up to 4 weeks rest, then a maintenance dose of 2 mg daily as hematologic recovery begins **or**

10 mg daily for 7-10 days; institute 2 mg daily maintenance dose after WBC >4000 cells/mm³ and platelets >100,000 cells/mm³ (~4-8 weeks); titrate maintenance dose to hematologic response **or**

0.15 mg/kg/day for 7 days, with a 2-6 week rest, followed by a maintenance dose of ≤0.05 mg/kg/day as hematologic recovery begins **or**

0.25 mg/kg/day for 4 days (or 0.2 mg/kg/day for 5 days); repeat at 4- to 6-week intervals as ANC and platelet counts return to normal

IV: 16 mg/m² administered at 2-week intervals for 4 doses, then administer at 4-week intervals after adequate hematologic recovery.

Ovarian carcinoma: Oral: 0.2 mg/kg/day for 5 days, repeat every 4-5 weeks **or**

Dosing: Adjustment for Possible Toxicity

Oral:

WBC <3000/mm³: Withhold treatment until recovery

Platelets <100,000/mm³: Withhold treatment until
recovery

I.V.: Adjust dose based on nadir blood cell counts

How Supplied: 2mg tablets

Precautions: nausea, vomiting, diarrhea; myelosuppression; hypersensitivity; renal toxicity; cardiotoxicity

Note Boxed Warnings: bone marrow suppression, hypersensitivity, leukemogenic

Drug Interactions: numerous, see product literature

hypertension, MI; with high-dose therapy), encephalopathy, hemolytic anemia, hemorrhagic cystitis, hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease; high-dose I.V. melphalan), hepatitis, infection, injection site reactions (ulceration, necrosis), interstitial pneumonitis, jaundice, mucositis (with high-dose therapy), ovarian suppression, paralytic ileus (with high-dose therapy), pruritus, pulmonary fibrosis, radiation myelopathy, rash (maculopapular), renal toxicity (with high-dose therapy), seizure (with high-dose therapy), sepsis, SIADH, skin hypersensitivity, sterility, stomatitis, testicular suppression, tingling sensation, transaminases increased, vasculitis, warmth sensation

Contraindications

Hypersensitivity to melphalan or any component of the formulation; patients whose disease

was resistant to prior melphalan therapy

Bone marrow suppression: **[U.S. Boxed Warning]: Bone marrow suppression is common; may be severe and result in infection or bleeding; has been demonstrated more with the I.V. formulation (compared to oral).** Myelosuppression is dose-related. Monitor blood counts; may require treatment delay or dose modification for thrombocytopenia or neutropenia. Use with caution in patients with prior bone marrow suppression, impaired renal function (consider dose reduction), or who have received prior (or concurrent) chemotherapy or irradiation. Myelotoxicity is generally reversible, although irreversible bone marrow failure has been reported. In patients who are candidates for autologous transplantation, avoid melphalan-containing regimens prior to transplant (due to the effects on stem cell reserve).

Hypersensitivity reactions: **[U.S. Boxed Warning]: Hypersensitivity reactions (including anaphylaxis) have occurred in ~2% of patients receiving I.V. melphalan,** usually after multiple treatment cycles. Discontinue infusion and treat symptomatically. Hypersensitivity may also occur (rarely) with oral melphalan. Do not readminister (oral or I.V.) in patients who experience hypersensitivity to melphalan.

Secondary malignancy: **[U.S. Boxed Warning]: Produces chromosomal abnormalities and is leukemogenic and potentially mutagenic.** Secondary malignancies (including acute myeloid leukemia, myeloproliferative disease, and carcinoma) have been reported (some patients were receiving combination chemotherapy or radiation therapy); the risk is increased with increased treatment duration and cumulative doses.

Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician**

Severe hypersensitivity to pemetrexed or any component of the formulation

References:

1. Alberts DS, Chang SY, Chen HS, et al, "Oral Melphalan Kinetics," *Clin Pharmacol Ther*, 1979, 26(6):737-45. [PubMed 498715]
2. Aronoff GR, Bennett WM, Berns JS, et al, *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 100.
3. Badros A, Barlogie B, Siegel E, et al, "Results of Autologous Stem Cell Transplant in Multiple Myeloma Patients With Renal Failure," *Br J Haematol*, 2001, 114(4):822-9. [PubMed 11564069]
4. Barlogie B, Kyle RA, Anderson KC, et al, "Standard Chemotherapy Compared With High-Dose Chemoradiotherapy for Multiple Myeloma: Final Results of Phase III US Intergroup Trial S9321," *J Clin Oncol*, 2006, 24(6):929-36. [PubMed 16432076]
5. Berthold F, Boos J, Burdach S, et al, "Myeloablative Megatherapy With Autologous Stem-Cell Rescue Versus Oral Maintenance Chemotherapy as Consolidation Treatment in Patients With High- Risk Neuroblastoma: A Randomised Controlled Trial," *Lancet Oncol*, 2005, 6(9):649-58. [PubMed 16129365]
6. Canete A, Gerrard M, Rubie H, et al, "Poor Survival for Infants with MYCN-Amplified Metastatic Neuroblastoma Despite Intensified Treatment: The International Society for Paediatric Oncology European Neuroblastoma Experience," *J Clin Oncol*, 2009, 27(7):1014-9. [PubMed 19171715]
7. Carlson K, Hjorth M, Knudsen LM, et al, "Toxicity in Standard Melphalan-Prednisone Therapy Among Myeloma Patients With Renal Failure - A Retrospective Analysis and Recommendations for Dose Adjustment," *Br J Haematol*, 2005, 128(5):631-5. [PubMed 15725084]
8. Colwill R, Crump M, Couture F, et al, "Mini-BEAM as Salvage Therapy for Relapsed or Refractory Hodgkin's Disease Before Intensive Therapy or Autologous Bone Marrow Transplantation," *J Clin Oncol*, 1995, 13(2):396-402. [PubMed 7844600]
9. Dimopoulos MA, Richardson PG, Schlag R, et al, "VMP (Bortezomib, Melphalan, and Prednisone) is Active and Well Tolerated in Newly Diagnosed Patients With Multiple Myeloma With Moderately Impaired Renal Function, and Results in Reversal of Renal Impairment: Cohort Analysis of the Phase III VISTA Study," *J Clin Oncol*, 2009, 27(36):6086-93. [PubMed 19858394]
10. Facon T, Mary JY, Hulin C, et al, "Melphalan and Prednisone Plus Thalidomide Versus Melphalan and Prednisone Alone or Reduced-Intensity Autologous Stem Cell Transplantation in Elderly Patients With Multiple Myeloma (IFM 99-06): A Randomised Trial," *Lancet*, 2007, 370(9594):1209-18. [PubMed 17920916]
11. Facon T, Mary JY, Pegourie B, et al, "Dexamethasone-Based Regimens versus Melphalan-Prednisone for Elderly Multiple Myeloma Patients Ineligible for High-Dose Therapy," *Blood*, 2006, 107(4):1292-8. [PubMed 16174762]
12. Femand JP, Katsahian S, Divine M, et al, "High-Dose Therapy and Autologous Blood Stem-Cell Transplantation Compared With Conventional Treatment in Myeloma Patients Aged 55 to 65 years: Long-Term Results of a Randomized Control Trial From the Group Myelome-Autogreffe," *J Clin Oncol*, 2005, 23(36):9227-33. [PubMed 16275936]
13. Griggs JJ, Mangu PB, Anderson H, et al, "Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline," *J Clin Oncol*, 2012, 30(13):1553-61. [PubMed 22473167]
14. Jaccard A, Moreau P, Leblond V, et al, "High-Dose Melphalan versus Melphalan Plus Dexamethasone for AL Amyloidosis," *N Engl J Med*, 2007, 357(11):1083-93. [PubMed 17855669]
15. Keefe DM, Schubert MM, Elting LS, et al, "Updated Clinical Practice Guidelines for the Prevention

- and Treatment of Mucositis," *Cancer*, 2007, 109(5):820-31. [PubMed 17236223]
16. King PD and Perry MC, "Hepatotoxicity of Chemotherapy," *Oncologist*, 2001, 6(2):162-76. [PubMed 11306728]
 17. Kintzel PE and Dorr RT, "Anticancer Drug Renal Toxicity and Elimination: Dosing Guidelines for Altered Renal Function," *Cancer Treat Rev*, 1995, 21(1):33-64. [PubMed 7859226]
 18. Martin A, Fernandez-Jimenez MC, Caballero MD, et al, "Long-Term Follow-Up in Patients Treated with Mini-BEAM as Salvage Therapy for Relapsed or Refractory Hodgkin's Disease," *Br J Haematol*, 2001, 113(1):161-71. [PubMed 11328296]
 19. Moreau P, Facon T, Attal M, et al, "Comparison of 200 mg/m² Melphalan and 8 Gy Total Body Irradiation Plus 140 mg/m² Melphalan as Conditioning Regimens for Peripheral Blood Stem Cell Transplantation in Patients With Newly Diagnosed Multiple Myeloma: Final Analysis of the Intergroupe Francophone du Myélome 9502 Randomized Trial," *Blood*, 2002, 99(3):731-5. [PubMed 11806971]
 20. Nath CE, Shaw PJ, Montgomery K, et al, "Population Pharmacokinetics of Melphalan in Pediatric Blood or Marrow Transplant Recipients," *Br J Clin Pharmacol*, 2007, 64(2):151-64. [PubMed 17324241]
 21. Nath CE, Shaw PJ, Trotman J, et al, "Population Pharmacokinetics of Melphalan in Patients With Multiple Myeloma Undergoing High Dose Therapy," *Br J Clin Pharmacol*, 2010, 69(5):484-97. [PubMed 20573084]
 22. National Institute for Occupational Safety and Health (NIOSH), "NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2012." Available at <http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf>. Accessed January 21, 2013.
 23. Oberlin O, Rey A, Desfachelles AS, et al, "Impact of High-Dose Busulfan Plus Melphalan as Consolidation in Metastatic Ewing Tumors: A Study by the Societe Francaise des Cancers de l'Enfant," *J Clin Oncol*, 2006, 24(24):3997-4002. [PubMed 16921053]
 24. Palladini G, Perfetti V, Obici L, et al, "Association of Melphalan and High-Dose Dexamethasone is Effective and Well Tolerated in Patients With AL (Primary) Amyloidosis Who are Ineligible for Stem Cell Transplantation," *Blood*, 2004, 103(8):2936-8. [PubMed 15070667]
 25. Palumbo A, Bringhen S, Caravita T, et al, "Oral Melphalan and Prednisone Chemotherapy Plus Thalidomide Compared With Melphalan and Prednisone Alone in Elderly Patients With Multiple Myeloma: Randomised Controlled Trial," *Lancet*, 2006, 367(9513):825-31. [PubMed 16530576]
 26. Palumbo A, Bringhen S, Liberati AM, et al, "Oral Melphalan, Prednisone, and Thalidomide in Elderly Patients With Multiple Myeloma: Updated Results of a Randomized Controlled Trial," *Blood*, 2008, 112(8):3107-14. [PubMed 18505783]
 27. Palumbo A, Bringhen S, Petrucci MT, et al, "Intermediate-Dose Melphalan Improves Survival of Myeloma Patients Aged 50 to 70: Results of a Randomized Controlled Trial," *Blood*, 2004, 104(10):3052-7. [PubMed 15265788]
 28. Pinguet F, Martel P, Rouanet P, et al, "Effect of Sodium Chloride Concentration and Temperature on Melphalan Stability During Storage and Use," *Am J Hosp Pharm*, 1994, 51(21):2701-4. [PubMed 7856585]
 29. Pritchard J, Cotterill SJ, Germond SM, et al, "High Dose Melphalan in the Treatment of Advanced Neuroblastoma: Results of a Randomised Trial (ENSG-1) by the European Neuroblastoma Study Group," *Pediatr Blood Cancer*, 2005, 44(4):348-57. [PubMed 15546135]
 30. San Miguel JF, Schlag R, Khuageva NK, et al, "Bortezomib Plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma," *New Engl J Med*, 2008, 359(9):906-17. [PubMed 18753647]

31. Schuh A, Dandridge J, Haydon P, et al, "Encephalopathy Complicating High-Dose Melphalan," *Bone Marrow Transplant*, 1999, 24(10):1141-3. [PubMed 10578165]
32. Seddon BM, Cassoni AM, Galloway MJ, et al, "Fatal Radiation Myelopathy After High-Dose Busulfan and Melphalan Chemotherapy and Radiotherapy for Ewing's Sarcoma: A Review of the Literature and Implications for Practice," *Clin Oncol*, 2005, 17(5):385-90. [PubMed 16097572]
33. Wadler S, Yeap B, Vogl S, et al, "Randomized Trial of Initial Therapy With Melphalan Versus Cisplatin-Based Combination Chemotherapy in Patients With Advanced Ovarian Carcinoma: Initial and Long Term Results -- Eastern Cooperative Oncology Group Study E2878," *Cancer*, 1996, 77(40):733-42. [PubMed 8616766]

Revision History:

Date Approved by P&T Committee: 10/22/13

Date Reviewed/No Updates: 1/28/14 by C. Sanders MD

Date Approved by P&T Committee: 1/28/14

Date Reviewed/No Updates: 1/13/15 by C. Sanders, MD

Date Approved by P&T Committee: 1/27/15

Date Reviewed/Updated: 7/7/15 by C. Sanders, MD; R. Sterling, MD

Date Approved by P&T Committee: 1/26/16

Date Reviewed/No Updates: 1/24/17 by C. Sanders, MD; R. Sterling, MD

Date Approved by P&T Committee: 1/24/17

Date Reviewed/No Updates: 1/23/18 by C. Sanders, MD; R. Sterling, MD

Date Approved by P&T Committee: 1/23/18

Date Reviewed/No Updates: 1/22/19 by C. Sanders, MD; R. Sterling, MD

Date Approved by P&T Committee: 1/22/19

Date Reviewed/No Updates: 2/18/20 by H. Taekman, MD; R. Sterling, MD

Date Approved by P&T Committee: 2/18/20

Revision Date	Content Revised (Yes/No)	Contributors	Review/Revision Notes
1/24/17	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/23/18	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/22/19	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
2/18/20	No	Howard Taekman, MD; Robert Sterling, MD	Annual review