TRUVEN HEALTH ANALYTICS™
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COMPENDIA TRANSPARENCY TRACKING FORM

DATE: 2/7/2017

PACKET: 1397

DRUG: Cyclophosphamide

USE: Graft versus host disease, Prophylaxis, As monotherapy in patients who have received matched related or unrelated bone marrow transplantation for high risk hematologic malignancies with a myeloablative conditioning regimen

COMPENDIA TRANSPARENCY REQUIREMENTS	
1	Provide criteria used to evaluate/prioritize the request (therapy)
2	Disclose evidentiary materials reviewed or considered
3	Provide names of individuals who have substantively participated in the review or disposition of the request and disclose their potential direct or indirect conflicts of interest
4	Provide meeting minutes and records of votes for disposition of the request (therapy)

EVALUATION/PRIORITIZATION CRITERIA: C, L, R, S *to meet requirement 1

CODE	EVALUATION/PRIORITIZATION CRITERIA
A	Treatment represents an established standard of care or significant **advance** over current therapies
C	**Cancer** or cancer-related condition
E	Quantity and robustness of **evidence** for use support consideration
L	**Limited** alternative therapies exist for condition of interest
P	**Pediatric** condition
R	**Rare** disease
S	**Serious**, life-threatening condition

Note: a combination of codes may be applied to fully reflect points of consideration [eg, therapy may represent an advance in the treatment of a life-threatening condition with limited treatment alternatives (ASL)]

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EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Luznik,L., Bolanos-Meade,J., Zahurak,M., et al: High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease. Blood Apr 22, 2010; Vol 115, Issue 16; pp. 3224-3230.	Comments: This was a phase 1/2 open-label study. There was low risk of bias associated with selection of cohorts and assessment of outcome. The analyses were conducted with the intent-to-treat population. The median follow-up was 29 months (range, 10-55 months) for surviving recipients of related donor grafts and 24 months (range, 14-48 months) for surviving recipients of unrelated donor grafts. A diagnosis of GVHD was confirmed pathologically and graded using standard criteria. Several potential confounding variables were analyzed. A major caveat of the study was the absence of a control group or active comparator.	S
Kanakry,C.G., O'Donnell,P.V., Furlong,T., et al: Multi-institutional study of post-transplantation cyclophosphamide as single-agent graft-versus-host disease prophylaxis after allogeneic bone marrow transplantation using myeloablative busulfan and fludarabine conditioning. Journal of Clinical Oncology Nov 01, 2014; Vol 32, Issue 31; pp. 3497-3505.	Comments: This was a multi-site, open-label, phase 2 study. There was low risk of bias associated with selection of cohorts and assessment of outcome. Acute GVHD was scored centrally by a third-party reviewer, using Modified Keystone Criteria. Chronic GVHD diagnosis and grading were based on National Institutes of Health criteria and were scored by third-party investigators at each participating institution. A pathologic confirmation of clinically suspected GVHD was obtained when possible. The median follow-up period of surviving patients was 794 days (2.2 years; range, 0.61 to 3.52 years). The analyses were conducted with the intent-to-treat population. Several potential confounding variables were analyzed. A major caveat of the study was the absence of a control group or active comparator.	S
Kanakry,C.G., Tsai,H.-L., Bolanos-Meade,J., et al: Single-agent GVHD prophylaxis with posttransplantation cyclophosphamide after myeloablative, HLA-matched BMT for AML, ALL, and MDS. Blood Dec 11, 2014; Vol 124, Issue 25; pp. 3817-3827.		3

Jacoby,E., Chen,A., Loeb,D.M., et al: Single-agent post-transplantation cyclophosphamide as graft-versus-host disease prophylaxis after human leukocyte antigen-matched related bone marrow transplantation for pediatric and young adult patients with hematologic malignancies. Biology of Blood and Marrow Transplantation 2016; Vol 22, Issue 1; pp. 112-118.		1
Pirogova,O., Moiseev,I., Alyanski,A., et al: Risk-adapted graft-versus-host disease prophylaxis with post-transplantation cyclophosphamide in related, unrelated and haploidentical stem cell transplantations. Bone Marrow Transplantation Mar 2016; Vol 51 SUPPL. 1, p. S185.		3
Mehta,R.S., Saliba,R.M., Chen,J., et al: Post-transplantation cyclophosphamide versus conventional graft-versus-host disease prophylaxis in mismatched unrelated donor haematopoietic cell transplantation. British Journal of Haematology May 01, 2016; Vol 173, Issue 3; pp. 444-455.		1
Alousi,A.M., Brammer,J.E., Saliba,R.M., et al: Phase II trial of graft-versus-host disease prophylaxis with post-transplantation cyclophosphamide after reduced-intensity busulfan/fludarabine conditioning for hematological malignancies. Biol Blood Marrow Transplant May 2015; Vol 21, Issue 5; pp. 906-912.		1

Rashidi,A., Slade,M., DiPersio,J.F., et al: Post-transplant high-dose cyclophosphamide after HLA-matched vs haploidentical hematopoietic cell transplantation for AML. Bone Marrow Transplantation 2016; Vol 51, pp. 1561-1564.		1
Mielcarek,M., Furlong,T., O'Donnell,P.V., et al: Posttransplantation cyclophosphamide for prevention of graft-versus-host disease after HLA-matched mobilized blood cell transplantation. Blood Mar 17, 2016; Vol 127, Issue 11; pp. 1502-1508.		1
Holtick,U., Chemnitz,J.-M., Shimabukuro-Vornhagen,A., et al: OCTET-CY: A phase II study to investigate the efficacy of post-transplant cyclophosphamide as sole graft-versus-host prophylaxis after allogeneic peripheral blood stem cell transplantation. European Journal of Haematology 2016; Vol 96, Issue 1; pp. 27-35.		1
Bradstock,K.F., Bilmon,I., Kwan,J., et al: Single-agent high-dose cyclophosphamide for graft-versus-host disease prophylaxis in human leukocyte antigen-matched reduced-intensity peripheral blood stem cell transplantation results in an unacceptably high rate of severe acute graft-versus-host disease. Biology of Blood and Marrow Transplantation 2015; Vol 21, Issue 5; pp. 934-953.		1

Literature evaluation codes: S = Literature selected; 1 = Literature rejected = Topic not suitable for scope of content; 2 = Literature rejected = Does not add clinically significant new information; 3 = Literature rejected = Methodology flawed/Methodology limited and unacceptable; 4 = Other (review article, letter, commentary, or editorial)

CONTRIBUTORS:

*to meet requirement 3

PACKET PREPARATION	DISCLOSURES	EXPERT REVIEW	DISCLOSURES
Felicia Gelsey, MS	None		
Stacy LaClaire, PharmD	None		
Catherine Sabatos, PharmD	None		
		John D Roberts	None
		Jeffrey Klein	None
		Richard LoCicero	Incyte Corporation Local PI for REVEAL. Study is a multicenter, non-interventional, non-randomized, prospective, observational study in an adult population for patients who have been diagnosed with clinically overt PV and are being followed in either community or academic medical centers in the US who will be enrolled over a 12-month period and observed for 36 months.

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	Evidence Favors Efficacy	Class IIa: Recommended, In Most Cases		B
John D Roberts	Evidence is Inconclusive	Class IIb: Recommended, In Some Cases	The reports suggest that high dose cyclophosphamide has some effectiveness. Two other reports conclude that high dose cyclophosphamide is not effective and dangerous when used in the similar, but not identical, situation of a peripheral blood stem cell transplantation (Bradstock, Biol Blood Marrow Transplant, 21:941, 2015; Alousi, Biol Blood Marrow Transplant, 21: 906, 2015). The presumed standard is cyclosporine plus methotrexate (plus antithymocyte globulin in the case of unrelated donor cells). The reports provide no evidence that high dose cyclophosphamide is better or worse than the presumed standard. Thus, high dose cyclophosphamide can only be recommended in unusual situations, for example, known intolerance to cyclosporine and/or methotrexate, or other standard regimens.	N/A

Jeffrey Klein	Evidence Favors Efficacy	Class I: Recommended	The use of high dose Cyclophosphamide as prophylaxis of GVHD in bone marrow transplant patients is quite effective. Long term efficacy was clearly demonstrated as well. Another benefit was the elimination in use of immunosuppressants in nearly half of patients tested. Adverse effects were not discussed however.	N/A
Richard LoCicero	Evidence Favors Efficacy	Class IIa: Recommended, In Most Cases	Single agent cyclophosphamide has been shown to be safe and effective in preventing graft versus host disease. Conclusions relative to comparisons to other prophylaxis is not possible due to its evaluation in these single arm trials.	N/A