TRUVEN HEALTH ANALYTICS™
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COMPENDIA TRANSPARENCY TRACKING FORM

DATE: 4/25/16

PACKET: 1285

DRUG: Antithymocyte Globulin Rabbit

USE: Graft versus host disease, prophylaxis in patients receiving unrelated donor hematopoietic stem cell transplantation for hematologic malignancies

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: A, C, 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
Ruutu T, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. Bone Marrow Transplant. 2014 Feb;49(2):168-73.		S
Walker,I., et al: Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial. Lancet Oncol Dec 23, 2015; Vol Epub, p. Epub.	Comments: This was an international, multicenter, open-label, randomised, phase 3 trial. Key bias criteria evaluated were (1) random sequence generation of randomization; (2) lack of allocation concealment, (3) lack of blinding, (4) incomplete accounting of patients and outcome events, and (5) selective outcome reporting bias. The study was at low risk of bias for these key criteria, and no additional biases were identified.	S
Theurich S, et al. Polyclonal anti-thymocyte globulins for the prophylaxis of graft-versus-host disease after allogeneic stem cell or bone marrow transplantation in adults (Review). Cochrane Library 2012, Issue 9.	Comments: This was a systematic review that included six randomized trials and a total of 568 patients investigating the impact of ATG on GVHD prophylaxis in adults suffering from hematological diseases and undergoing allogeneic HSCT.. The risk of bias tool was used to assess the quality of the included trials. According to the authors, the overall risk of bias was judged to be moderate in the included six studies. This systematic review conducted a comprehensive literature search and provided information on eligibility criteria, study characteristics, and heterogeneity. The appropriate statistical tests were used.	1
Kumar A et al. Antithymocyte globulin for acute-graft-versus-host-disease prophylaxis in patients undergoing allogeneic hematopoietic cell transplantation: a systematic review. Leukemia (2012) 26, 582–588.	Comments: This was a systematic review that included seven randomized trials and a total of 733 patients comparing ATG versus control for prevention of GVHD in patients undergoing allo-HCT. The methodological quality of the studies was assessed by examining methodological domains relevant to minimizing bias and random error. This systematic review conducted a comprehensive literature search and provided information on eligibility criteria, study characteristics, and heterogeneity. The appropriate statistical tests were used.	1

Theurich S et al. Anti-thymocyte globulins for post-transplant graft-versus-host disease prophylaxis—A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology 88 (2013) 178–186.	Comments: This was a systematic review that included six randomized trials and a total of 568 patients comparing the addition of ATG to standard immunosuppressive regimen as GvHD prophylaxis. The risk of bias tool was used to assess the quality of the included trials. According to the authors, the overall risk of bias was judged to be moderate in the included six studies. This systematic review conducted a comprehensive literature search and provided information on eligibility criteria, study characteristics, and heterogeneity. The appropriate statistical tests were used.	1
Ziakas,P.D., et al: Graft-versus-host disease prophylaxis after transplantation: A network meta-analysis. PLoS ONE [Electronic Resource] Dec 2014; Vol 9, Issue 12; p. e114735.		1
Du K et al. Long-term outcomes of antithymocyte globulin in patients with hematological malignancies undergoing myeloablative allogeneic hematopoietic cell transplantation: a systematic review and meta-analysis. Clin Transplant 2013: 27: E91–E100		1
Socie,G., et al: Chronic graft-versus-host disease: long-term results from a randomized trial on graft-versus-host disease prophylaxis with or without anti-T-cell globulin ATG-Fresenius. Blood Jun 09, 2011; Vol 117, Issue 23; pp. 6375-6382.		1
Finke,J., et al: Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial. Lancet Oncol Sep 2009; Vol 10, Issue 9; pp. 855-864.		1

Bacigalupo,A et al. Pre-emptive treatment of acute GVHD: a randomized multicenter trial of rabbit anti-thymocyte globulin, given on dayþ7 after alternative donor transplants. Bone Marrow Transplantation (2010) 45, 385–391.	Comments: This was a multicenter, open-label, randomized trial. Overall, this study was at low risk of biases associated with lack of blinding, incomplete accounting of patients and outcome events, and selective outcome reporting. The risk of bias associated with random sequence generation and allocation concealment was unclear and not discussed in the paper.	1
Bacigalupo,A., et al: Antithymocyte globulin for graft-versus-host disease prophylaxis in transplants from unrelated donors: 2 randomized studies from Gruppo Italiano Trapianti Midollo Osseo (GITMO). Blood Nov 15, 2001; Vol 98, Issue 10; pp. 2942-2947.	Comments: One hundred nine patients were randomized in two consecutive multicenter trials testing the effect of ATG in the conditioning regimen, given in two different doses, compared with patients receiving no ATG. Each center in the study used the same conditioning regimen. The results of the two RCTs were presented separately. Overall, the trials were at low risk of biases associated with allocation concealment, lack of blinding, incomplete accounting of patients and outcome events, and selective outcome reporting. The risk of bias associated with random sequence generation was unclear and not discussed in the paper.	2
Bacigalupo,A., et al: Thymoglobulin prevents chronic graft-versus-host disease, chronic lung dysfunction, and late transplant-related mortality: long-term follow-up of a randomized trial in patients undergoing unrelated donor transplantation. Biology of Blood & Marrow Transplantation May 2006; Vol 12, Issue 5; pp. 560-565.	Comments: One hundred nine patients were randomized in two consecutive multicenter trials testing the effect of ATG in the conditioning regimen, given in two different doses, compared with patients receiving no ATG. Each center in the study used the same conditioning regimen. The results of the two RCTs were presented separately. Overall, the trials were at low risk of biases associated with allocation concealment, lack of blinding, incomplete accounting of patients and outcome events, and selective outcome reporting. The risk of bias associated with random sequence generation was unclear and not discussed in the paper.	2
Hannon,M., et al: Immune recovery after allogeneic hematopoietic stem cell transplantation following flu-TBI versus TLI-ATG conditioning. Clin Cancer Res 2015; Vol 21, Issue 14; pp. 3131-3139.		1
Doney, K.C., et al: Treatment of graft-versus-host disease in human allogeneic marrow graft recipients: a randomized trial comparing antithymocyte globulin and corticosteroids. Am J Hematol 1981; Vol 11, Issue 1; pp. 1-8.		1

Kroger N et al. Anti-Thymocyte-Globulin as part of the preparative regimen prevents graft failure and severe Graft versus Host disease (GvHD) in allogeneic stem cell transplantation from unrelated donors. Ann Hematol (2001) 80:209–215		3
Bacigalupo,A., et al: Pre-emptive therapy of acute graft-versus-host disease: a pilot study with antithymocyte globulin (ATG). Bone Marrow Transplant Dec 2001; Vol 28, Issue 12; pp. 1093-1096.		3

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		
		Jeffrey Klein	None
		Dina Dumercy	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 I: Recommended		B
Jeffrey Klein	Evidence Favors Efficacy	Class I: Recommended	The use of antithymocyte globulin rabbit as a prophylaxis of GVHD in patients undergoing allogenic stem cell transplant showed a significant benefit. In addition the product demonstrated a decrease need for the use of immunosuppressive agents in these patients. Concern over infusion reactions needs to be addressed further as does the concern over Epstein Barr Virus reactivation and its subsequent management.	N/A

Dina Dumercy	Evidence Favors Efficacy	Class I: Recommended	Anti-thymocyte globulin (ATG) has been shown in two randomised trials to decrease the incidence of CGVHD around 1 year after transplantation without adversely affecting the incidence of disease relapse, serious infection, or overall survival. The Walker 2015, phase 3, multicentre, open-label, randomised controlled trial at ten transplant centres in 203 patient that showed 37 (37%) of 99 patients who received ATG were free from immunosuppressive treatment at 12 months compared with 16 (16%) of 97 who received no ATG (adjusted odds ratio 4·25 [95% CI 1·87–9·67]; p=0·00060. This supports the previous off label use and guideline recommended use, while adding more evidence to the patient benefit from Rabbit Anti-thymocyte globulin being added to the backbone of prophylaxis against GVHD. The recommended dose is lower (4.5 mg/kg) than previously use (7.5 mg/kg) and more studies should be done to find the optimal dose and schedule of Rabbit Anti-thymocyte globulin.	N/A
Richard LoCicero	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	ATG has been shown in at least one phase III randomized trial that treatment reduces the need for immunosuppressive therapy at 12 months after transplant without an increase in toxicity or malignancy relapse. The incorporation of ATG into a regimen to prevent chronic graft vs. host disease is reasonable.	N/A