TRUVEN HEALTH ANALYTICS™
an IBM Company

COMPENDIA TRANSPARENCY TRACKING FORM

DATE: 9/21/16

PACKET: 1348

DRUG: Isotretinoin

USE: Neuroblastoma, high-risk, newly diagnosed, as post-consolidation therapy

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, P, 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)]

TRUVEN HEALTH ANALYTICS™
an IBM Company

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Matthay,K.K., et al: Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A children's oncology group study. Journal of Clinical Oncology 2009; Vol 27, Issue 7; pp. 1007-1013.	Comments: This was a single-blind randomized trial that included two separate sequential random assignments in a quasi-factorial design. 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
Matthay, KK, et al: Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. New England Journal of Medicine 1999; Vol 341, Issue 16; pp. 1165-1173.		S
Parikh NS, et al; International Society of Pediatric Oncology. SIOP-PODC adapted risk stratification and treatment guidelines: Recommendations for neuroblastoma in low- and middle-income settings. Pediatr Blood Cancer. 2015 Aug;62(8):1305-16.		S
Matthay, KK, et al: Errata: long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. J Clin Oncol Jun 10, 2014; Vol 32, Issue 17; pp. 1862-1863.		S

Peinemann,F., van Dalen,E.C., and Berthold,F.: Retinoic Acid for High-risk Neuroblastoma Patients after Autologous Stem Cell Transplantation - Cochrane Review. Klin.Padiatr. Apr 2016; Vol 228, Issue 3; pp. 124-129.		1
Peinemann F, van Dalen EC, Tushabe DA, Berthold F. Retinoic acid post consolidation therapy for high-risk neuroblastoma patients treated with autologous hematopoietic stem cell transplantation. Cochrane Database Syst Rev. 2015 Jan 29;1:CD010685.	Comments: This was a Cochrane systematic review that included eight publications associated with one RCT(CCG-3891). The risk of bias tool was used to assess the quality of the included trial. Overall, the study was at both low risk and unclear risk for many of the risk of bias criteria. 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
Chen,S.C., et al: Predicting, Monitoring, and Managing Hypercalcemia Secondary to 13-Cis-Retinoic Acid Therapy in Children with High-risk Neuroblastoma. Journal of Pediatric Hematology/Oncology 2015; Vol 37, Issue 6; pp. 477-481.		4
Kohler, Imeson, Ellerhaw. A randomized trial of 13-cis-retinoic acid in children with advanced neuroblastoma after high-dose therapy. Br J Cancer 2000. 83(9):1124-7.		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		
		Adam Levy	None
		Lindsey Roke	None
		Rachelle Nuss	Company Name: MSTX A randomized controlled double-blind study of Polaxamer-88 for treatment of vaso-occlusive crisis in sickle cell.

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases		B
Adam Levy	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	The optimal therapy for high risk neuroblastoma remains elusive. Isotretinoin showed early promise with improved event free survival at 3 years, but that improvement was not sustained at longer follow-up. As such, there is evidence that suggests some efficacy, but this cannot be considered standard of care and isotretinoin has not been included in all subsequent clinical trials for high risk neuroblastoma.	N/A

Lindsey Roke	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	I believe that in the situations described in the literature (post-consolidation therapy in patients with high-risk neuroblastoma in complete remission following chemotherapy and ASCT), this treatment is warranted. Though OS was not significantly better using isotretinoin, there was a trend towards improved survival. Since this was only studied as post-consolidation therapy, I do not believe we should recommend this in all cases. For the patients described in the studies, though, I feel that this could be beneficial.	N/A
Rachelle Nuss	Effective	Class I: Recommended	Literature going back 17 years indicates event-free survival (EFS) three years after receiving isotretinoin as consolidation, compared with not receiving it, following bone marrow transplant or chemotherapy for high risk neuroblastoma, is improved for children. A 2009 publication evaluating EFS at 5 years did not demonstrate a significant improvement but a 2010 study (Alice L. Yu, M.D., Ph.D., Andrew L. Gilman, M.D., M. Fevzi.N Engl J Med 2010; 363:1324-1334) comparing isotretinoin to Anti-GD2 Antibody with GM-CSF, Interleukin-2, and Isotretinoin for Neuroblastoma again showed EFS of 46% at 2 years which is significantly better than without it. In addition, combining isotretinoin with anti-GD2 antibody and GM-CSF and interleukin-2 improves EFS further.	N/A