COMPENDIA TRANSPARENCY TRACKING FORM

DATE: October 31, 2024

OFF-LABEL ID #: 2742

DRUG NAME: Methotrexate Sodium

OFF-LABEL USE: Immune effector cell-associated neurotoxicity syndrome Steroid refractory, in patients treated with CAR-T cell 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: L, 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)]

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	LITERATURE CODE
Strati, P, Horowitz, S, Primeaux, B, et al: Use of Intrathecal Chemotherapy for Corticosteroid-Refractory Icans in B-Cell Lymphoma Patients Treated with CART. Transplant Cell Ther Feb 2024; Vol 30, Issue 2 Suppl; p. S365.	S
Bashey SZ, Solomon SR, Zhang X, Morris LE, Holland HK, Bachier L, Patel K, Solh MM. Intrathecal chemotherapy as treatment for chimeric antigen receptor T cell (CAR T) therapy associated neurotoxicity. Bone Marrow Transplant. 2024 Sep 19. doi: 10.1038/s41409-024-02417-w. Epub ahead of print. PMID: 39300248.	S
Solh, MM, Bashey, A, Morris, L, et al: Intrathecal Chemotherapy As Treatment for Chimeric Antigen Receptor T Cell (CAR T) Therapy Associated Neurotoxicity. Blood 2023; Vol 142, Issue Supp 1; p. 2138.	2
Yucebay, F, Maakaron, J, Grana, A, et al: Intrathecal chemotherapy: an alternative treatment strategy to prolonged corticosteroids for severe CAR T associated neurotoxicity. Biol Blood Marrow Transplant 2020; Vol 26, Issue 3; p. S312.	S
Asawa, P, Vusqa, U, Khan, C, et al: Intrathecal Chemotherapy as a Potential Treatment for Steroid-refractory Immune Effector Cell-associated Neurotoxicity Syndrome. Anticancder Res Aug 2022; Vol 42, Issue 8; pp. 3853-3856.	2
Shah, NN, Johnson, BD, Fenske, TS, et al: Intrathecal chemotherapy for management of steroid-refractory CAR T-cell-associated neurotoxicity syndrome. Blood Adv May 26, 2020; Vol 4, Issue 10; pp. 2119-2122. Pubmed ID: 32407473	2
Katsin, M, Shman, T, Migas, A, et al: Case report: rapid resolution of grade IV ICANS after first line intrathecal chemotherapy with methotrexate, cytarabine and dexamethasone. Front Immunol May 03, 2024; Vol 15, p. 1380451. Pubmed ID: 38765003	2
Shalabi, H, Harrison, C, Yates, B, et al: Intrathecal hydrocortisone for treatment of children and young adults with CAR T-cell immune-effector cell-associated neurotoxicity syndrome. Pediatr Blood Cancer Jan 2024; Vol 71, Issue 1; p. e30741. Pubmed ID: 37897136	1
Zurko, JC, Johnson, BD, Aschenbrenner, E, et al: Use of Early Intrathecal Therapy to Manage High-Grade Immune Effector Cell-Associated Neurotoxicity Syndrome. JAMA Oncol May 01, 2022; Vol 8, Issue 5; pp. 773-775. Pubmed ID: 35266965	1
Hayden, PJ, Roddie, C, Bader, P, et al: Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation	S

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
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
MERATIVE MICROMEDEX	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases		B
Jeffrey Klein	Evidence Favors Efficacy	Class IIa: Recommended, in Most Cases	The use of low dose Methotrexate intrathecally to treat neurotoxicity syndrome for patients that have received CAR-T therapy is effective. Resolution of the symptoms was observed in this small study. These patients had previously received steroids but were refractory to them.	
Todd Gersten	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	The limited, almost anecdotal, use of MTX in steroid refractory ICANS suggests that it may be an effective therapy.	

Warren Brenner	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	These small retrospective studies show that the administration of IT methotrexate +cytarabine and hydrocortisone can be effective in this difficult patient population with severe ICANS. The data shows efficacy but given the small sample size and retrospective nature of the studies I gave it an efficacy rating of favoring efficacy. Given the complexity of these patients and multiple compounding issues such as type of malignancy, type of CAR T product received as well as small numbers of patients and retrospective studies I would recommend this in some cases as the data is in early phase and there is non randomization between different treatments I would recommend in some cases that it would be a valid treatment option	