TRUVEN HEALTH ANALYTICS

COMPENDIA TRANSPARENCY TRACKING FORM

DATE: **JUNE 2015**

PACKET: **1234**

DRUG: **Melphalan Hydrochloride**

INDICATION: **Retinoblastoma [Pediatrics]**

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, E, L, P, 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)]

TRUVEN HEALTH ANALYTICS

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

CITATION	STUDY-SPECIFIC COMMENTS	LITERATURE CODE
Suzuki,S., Aihara,Y., Fujiwara,M., et al: Intravitreal injection of melphalan for intraocular retinoblastoma. Japanese Journal of Ophthalmology 2015; Vol Epub, p. Epub.	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	S
Francis,J.H., Abramson,D.H., Gaillard,M.-C., et al: The Classification of Vitreous Seeds in Retinoblastoma and Response to Intravitreal Melphalan. Ophthalmology 2015; Vol Epub, p. Epub.	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	S
Suzuki,S., et al: Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: The long-term prognosis. Ophthalmology Oct 2011; Vol 118, Issue 10; pp. 2081-2087	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	3
Gobin,Y.P., et al: Intra-arterial chemotherapy for the management of retinoblastoma four-year experience. Archives of Ophthalmology Jun 2011; Vol 129, Issue 6; pp. 732-737.	This was an open-label single-arm study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered prospectively. All subjects were analyzed.The results should be interpreted with caution since the study lacked a control group.1	S

Shields,C.L., et al: Intra-arterial chemotherapy for retinoblastoma in 70 eyes: Outcomes based on the international classification of retinoblastoma. Ophthalmology Jul 2014; Vol 121, Issue 7; pp. 1453-1460.	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	S
Marr,B.P.: Success of intra-arterial chemotherapy (chemosurgery) for retinoblastoma: effect of orbitovascular anatomy. Archives of Ophthalmology Feb 2012; Vol 130, Issue 2; pp. 180-185.	This was 2a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	1
Abramson,D.H., et al: Ophthalmic artery chemosurgery for less advanced intraocular retinoblastoma: Five year review. PLoS ONE [Electronic Resource] Apr 2012; Vol 7, Issue 4; p. 1.	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Although the authors did not specifiy if the data was gathered from medical records, they did state the outcomes were measured before and after both dilation and undergoing anesthesia. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	2
Venturi,C.: Superselective ophthalmic artery infusion of melphalan for intraocular retinoblastoma: preliminary results from 140 treatments. Acta Opthalmologica Jun 2013; Vol 91, Issue 4; pp. 335-342.	This was an open-label single-arm study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered prospectively. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	S
Francis,J.H., et al: Efficacy and Toxicity of Second-Course Ophthalmic Artery Chemosurgery for Retinoblastoma. Ophthalmology 2015;	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	S

Phillips,T.J., et al: Autonomic cardio-respiratory reflex reactions and superselective ophthalmic arterial chemotherapy for retinoblastoma. Paediatric anaesthesia Oct 2013; Vol 23, Issue 10; pp. 940-945.	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed.	2
Munier,F.L., et al: Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: From prohibition to conditional indications. British journal of ophthalmology 2012; Vol 96, Issue 8; pp. 1078-1083.	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	3
Francis,J.H.: Local and systemic toxicity of intravitreal melphalan for vitreous seeding in retinoblastoma: a preclinical and clinical study. Ophthalmology Sep 2014; Vol 121, Issue 9; pp. 1810-1817.	This was an open-label, single-arm, phase ll trial. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered prospectively. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	3
Ghassemi,F.: Intravitreal melphalan for refractory or recurrent vitreous seeding from retinoblastoma. Archives of Ophthalmology Oct 2012; Vol 130, Issue 10; pp. 1268-1271.	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	3
Ghassemi,F.: Combined intravitreal melphalan and topotecan for refractory or recurrent vitreous seeding from retinoblastoma. JAMA Ophthalmology Aug 2014; Vol 132, Issue 8; pp. 936-941	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	3

Shields,C.L., et al: Intravitreal melphalan for persistent or recurrent retinoblastoma vitreous seeds: Preliminary results. JAMA Ophthalmology Mar 2014; Vol 132, Issue 3; pp. 319-325.	This was a retrospective study. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered from medical records. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	3
Smith,S.J., Smith,B.D., and Mohney,B.G.: Ocular side effects following intravitreal injection therapy for retinoblastoma: A systematic review. British journal of ophthalmology 2014; Vol 98, Issue 3; pp. 292-297.		S
Smith SJ & Smith BD. Evaluating the risk of extraocular tumour spread following intravitreal injection therapy for retinoblastoma: a systematic review. Br J Ophthalmol 2013;97:1231-1236.		S
Araki,Y., et al: Secondary neoplasms after retinoblastoma treatment: Retrospective cohort study of 754 patients in Japan. Japanese Journal of Clinical Oncology Mar 2011; Vol 41, Issue 3; pp. 373-379.		1
Gunduz,K., et al: Retinoblastoma in Turkey: Results from a tertiary care center in Ankara. Journal of Pediatric Ophthalmology and Strabismus Sep 2013; Vol 50, Issue 5; pp. 296-303.		1

Klufas,M.A., et al: Intra-arterial chemotherapy as a treatment for intraocular retinoblastoma: Alternatives to direct ophthalmic artery catheterization. American Journal of Neuroradiology 2012; Vol 33, Issue 8; pp. 1608-1614.		1
Akiyama,M., et al: Reduced cycles of systemic chemotherapy with following more focused local treatments for intraocular retinoblastoma. Pediatric Blood and Cancer Dec 2012; Vol 59, Issue 6; p. 1063.		1
Okimoto,S. and Nomura,K.: Clinical manifestations and treatment of retinoblastoma in kobe children's hospital for 16 years. Journal of Pediatric Ophthalmology and Strabismus 2014; Vol 51, Issue 4; pp. 222-229.		1
Palioura,S., et al: Ophthalmic artery chemosurgery for the management of retinoblastoma in eyes with extensive (>50%) retinal detachment. Pediatric Blood and Cancer Nov 2012; Vol 59, Issue 5; pp. 859-864.		1
Taich,P.: Clinical pharmacokinetics of intra-arterial melphalan and topotecan combination in patients with retinoblastoma. Ophthalmology Apr 2014; Vol 121, Issue 4; pp. 889-897.	This was an open-label, single-arm, phase ll trial. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered prospectively. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	2

Marr,B.P., et al: Three-drug intra-arterial chemotherapy using simultaneous carboplatin, topotecan and melphalan for intraocular retinoblastoma: Preliminary results. British journal of ophthalmology 2012; Vol 96, Issue 10; pp. 1300-1303.		2
Rojanaporn,D.: Intravenous chemoreduction or intra-arterial chemotherapy for cavitary retinoblastoma: long-term results. Archives of Ophthalmology May 2012; Vol 130, Issue 5; pp. 585-590.		1
Abramson,D.H., et al: Superselective ophthalmic artery chemotherapy as primary treatment for retinoblastoma (chemosurgery). Ophthalmology Aug 2010; Vol 117, Issue 8; pp. 1623-1629.	This was an open-label, single-arm, phase ll trial. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered prospectively. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	2
Shields,C.L., et al: Intra-arterial chemotherapy for retinoblastoma: Report no. 1, control of retinal tumors, subretinal seeds, and vitreous seeds. Archives of Ophthalmology Nov 2011; Vol 129, Issue 11; pp. 1399-1406.		2

Thampi,S., et al: Superselective intra-arterial melphalan therapy for newly diagnosed and refractory retinoblastoma: Results from a single institution. Clinical Ophthalmology May 24, 2013; Vol 7, pp. 981-989.		2
Schaiquevich,P.: Intra-arterial chemotherapy is more effective than sequential periocular and intravenous chemotherapy as salvage treatment for relapsed retinoblastoma. Pediatric blood & cancer May 2013; Vol 60, Issue 5; pp. 766-770.		2
Peterson,E.C., et al: Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: Initial experience with 17 tumors. Journal of neurosurgery Jun 2011; Vol 114, Issue 6; pp. 1603-1608.	This was an open-label, single-arm, phase II trial. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered prospectively. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	2
Muen,W.J., et al: Efficacy and complications of super-selective intra-ophthalmic artery melphalan for the treatment of refractory retinoblastoma. Ophthalmology Mar 2012; Vol 119, Issue 3; pp. 611-616.	This was an open-label, single-arm, phase II trial. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered prospectively. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group and tumor control was not defined.	2

Shields,C.L., et al: Management of advanced retinoblastoma with intravenous chemotherapy then intra-arterial chemotherapy as alternative to enucleation. Retina Nov 2013; Vol 33, Issue 10; pp. 2103-2109.		2
Kingston,J., et al: Intra-arterial melphalan chemotherapy in relapsed retinblastoma is an effective salvage therapy and a safe alternative to external beam radiotherapy. Pediatric Blood and Cancer 2012; Vol 59, Issue 6; pp. 985-986.	Abstract	4
Lee,S.H., et al: Tandem high-dose chemotherapy and autologous stem cell rescue in children with bilateral advanced retinoblastoma. Bone Marrow Transplantation 2008; Vol 42, Issue 6; pp. 385-391.		1
Ong,S.J., et al: Selective ophthalmic arterial injection of melphalan for intraocular retinoblastoma: a 4-year review. Jpn J Ophthalmol Dec 03, 2014		2
Tsimpida,M.: Visual outcomes following intraophthalmic artery melphalan for patients with refractory retinoblastoma and age appropriate vision. British journal of ophthalmology Nov 2013; Vol 97, Issue 11; pp. 1464-1470		2

Parareda,A.: Intra-arterial chemotherapy for retinoblastoma. Acta Opthalmologica May 2014; Vol 92, Issue 3; pp. 209-215.	This was an open-label, single-arm, phase ll trial. The trial ended prematurely due to difficulty with patient accrual. There was low risk of bias associated with selection of patients and assessment of outcomes. Data was gathered prospectively. All subjects were analyzed. The results should be interpreted with caution since the study lacked a control group.	2
Palma,J.: Successful treatment of metastatic retinoblastoma with high-dose chemotherapy and autologous stem cell rescue in South America. Bone Marrow Transplantation Apr 2012; Vol 47, Issue 4; pp. 522-527.		1
Abramson,D.H., et al: A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma. Initial results. Ophthalmology Aug 2008; Vol 115, Issue 8; pp. 1398-1404.		2
Vajzovic,L.M., et al: Supraselective intra-arterial chemotherapy: Evaluation of treatment-related complications in advanced retinoblastoma. Clinical Ophthalmology 2011; Vol 5, Issue 1; pp. 171-176.		2
Shields,C.L., et al: Minimal exposure (one or two cycles) of intra-arterial chemotherapy in the management of retinoblastoma. Ophthalmology Jan 2012; Vol 119, Issue 1; pp. 188-192.		1

Gonzalez Monroy,J.E., Orbach,D.B., and VanderVeen,D.: Complications of intra-Arterial chemotherapy for retinoblastoma. Seminars in ophthalmology 2014; Vol 29, Issue 5-6; pp. 429-433.		4
Dunkel, I.J., et al: Risk factors for severe neutropenia following intra-arterial chemotherapy for intra-ocular retinoblastoma. PLoS ONE Oct 2014; Vol 9, Issue 10; p. 1.		1
Francis,J.H., et al: Electroretinogram monitoring of dose-dependent toxicity after ophthalmic artery chemosurgery in retinoblastoma eyes: Six year review. PLoS ONE [Electronic Resource] Jan 2014; Vol 9, Issue 1; p. 1.		1
Phillips,T., et al: Myocardial Stun phenomenon during intra-ophthalmic artery chemotherapy for relapsed retinoblastoma treatment. Paediatric anaesthesia Sep 2012; Vol 22, Issue 9; p. 926.		2
Munier,F.L.: Occurrence of sectoral choroidal occlusive vasculopathy and retinal arteriolar embolization after superselective ophthalmic artery chemotherapy for advanced intraocular retinoblastoma. Retina Mar 2011; Vol 31, Issue 3; pp. 566-573.		2

Steinle,J.J., et al: Intra-ophthalmic artery chemotherapy triggers vascular toxicity through endothelial cell inflammation and leukostasis. Investigative Ophthalmology and Visual Science Apr 2012; Vol 53, Issue 4; pp. 2439-2445.		1
Shields,C.L., et al: Intra-arterial chemotherapy for retinoblastoma: Report no. 2, treatment complications. Archives of Ophthalmology Nov 2011; Vol 129, Issue 11; pp. 1407-1415.		2
Nath,C.E., et al: Melphalan pharmacokinetics in children with malignant disease: Influence of body weight, renal function, carboplatin therapy and total body irradiation. British Journal of Clinical Pharmacology 2005; Vol 59, Issue 3; pp. 314-324.		1
Nath,C.E., et al: Population pharmacokinetics of melphalan in paediatric blood or marrow transplant recipients. British Journal of Clinical Pharmacology 2007; Vol 64, Issue 2; pp. 151-164.		1

Schaiquevich,P.: Pharmacokinetic analysis of melphalan after superselective ophthalmic artery infusion in preclinical models and retinoblastoma patients. Investigative Ophthalmology & Visual Science 2012; Vol 53, Issue 7; pp. 4205-4212.		1
Schaiquevich,P., et al: Clinical pharmacokinetics of melphalan after super-selective ophthalmic artery infusion in retinoblastoma patients. Therapeutic Drug Monitoring Oct 2013; Vol 35, Issue 5; p. 713.		1
Chung,C.Y., et al: Retinoblastoma: Evidence for stage-based chemotherapy. International Ophthalmology Clinics 2015; Vol 55, Issue 1; pp. 63-75.		4
Shields,C.L., et al: Retinoblastoma frontiers with intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Eye Feb 27, 2013; Vol 27, Issue 2; pp. 253-264.		4
Dimaras,H., et al: Retinoblastoma. The Lancet Apr 2012; Vol 379, Issue 9824; pp. 1436-1440.		4
Zanaty,M., et al: Update on intra-arterial chemotherapy for retinoblastoma. Scientific World Journal 2014; Vol 2014, Issue 869604; p. 1.		4

Shields,C.L., et al: Targeted retinoblastoma management: when to use intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Curr Opin Ophthalmol Sep 2014; Vol 25, Issue 5; pp. 374-385.		4
Ghassemi,F., et al: Regression patterns in treated retinoblastoma with chemotherapy plus focal adjuvant therapy. Pediatric Blood and Cancer Apr 2013; Vol 60, Issue 4; pp. 599-604.		1
Ghassemi,F.: Pathological findings in enucleated eyes after intravitreal melphalan injection. International Ophthalmology Jun 2014; Vol 34, Issue 3; pp. 533-540.		1
Buitrago,E., et al: Stability of melphalan solution for intravitreal injection for retinoblastoma. JAMA Ophthalmol Nov 2014; Vol 132, Issue 11; pp. 1372-1373.		1
Shields,C.L., et al: Retinoblastoma frontiers with intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Eye Feb 27, 2013; Vol 27, Issue 2; pp. 253-264.		4
Munier,F.L et al: Intravitreal chemotherapy for vitreous seeding in retinoblastoma: Recent advances and perspectives. Saudi Journal of Ophthalmology Jul 2013; Vol 27, Issue 3; pp. 147-150.		4

Shields,C.L., et al: Targeted retinoblastoma management: when to use intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Curr Opin Ophthalmol Sep 2014; Vol 25, Issue 5; pp. 374-385.		4

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
Margi Schiefelbein, PA	None	Edward Balaban, DO	None
Stacy LaClaire, PharmD	None	James E. Liebmann, MD	None
Felicia Gelsey, MS	None	Jeffrey A. Bubis, DO	None
		Jeffrey Patton, MD	None
		Thomas Marsland, MD	None

ASSIGNMENT OF RATINGS:

*to meet requirement 4

	EFFICACY	STRENGTH OF RECOMMENDATION	COMMENTS	STRENGTH OF EVIDENCE
MICROMEDEX	---	---		B
Edward Balaban, DO	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	At least IIb. I suspect could be IIa – lack of control groups and I suspect some underlying selection bias.	N/A

James E. Liebmann, MD	Evidence Favors Efficacy	Class IIb: Recommended, in Some Cases	The articles for review document a high level of activity of intra-arterial (IA) melphalan as treatment of retinoblastoma. These findings come from several centers and are consistent. IA melphalan is a reasonable option for treatment of retinoblastoma, particularly if eye preservation is an important consideration. It should only be performed at a center where clinicians have experience with the procedure. Intravitreal melphalan also seems to be a safe, reasonable option for patients with documented intravitreal spread of retinoblastoma. Intravitreal administration of melphalan should only be performed at a center where clinicians have experience with the procedure.	N/A
Jeffrey A. Bubis, DO	Evidence Favors Efficacy	Class IIb: Recommended, In Some Cases	Non-randomized data. Very promising. Risk: benefit ratio not clear without randomized trials for all patients.	N/A
Jeffrey Patton, MD	Evidence Favors Efficacy	Class IIa: Recommended, in Most Cases	None	N/A
Thomas Marsland, MD	Evidence Favors Efficacy	Class IIa: Recommended, In Most Cases	Several studies including meta analyses suggest effectiveness with acceptable toxicity. No randomized trials, but is a rare tumor and this is only for a select subset of those patients.	N/A