MEDICAL POLICY

SUBJECT: ISOLATED LIMB PERFUSION and INFUSION	**EFFECTIVE DATE: 01/17/02** **REVISED DATE: 09/19/02, 11/20/03, 11/18/04, 09/15/05, 07/20/06, 09/20/07, 08/21/08, 07/16/09, 08/19/10** **ARCHIVED DATE: 08/18/11** **EDITED DATE: 09/20/12, 09/19/13, 09/18/14, 09/17/15, 09/15/16, 09/21/17, 09/20/18**
POLICY NUMBER: 7.01.52 **CATEGORY: Technology Assessment**	**PAGE: 1 OF: 6**

- ***If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.***
- ***If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.***
- ***If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.***

POLICY STATEMENT:

Based upon our criteria and assessment of peer-reviewed literature:

I. Isolated Limb Perfusion/Infusion has been medically proven to be effective and therefore **medically appropriate** in the treatment of patients with local recurrence of *unresectable* melanoma.

II. Isolated Limb Perfusion/Infusion as an adjuvant treatment in patients with resectable *primary* melanoma who have no other clinical evidence of the disease does not improve patient outcomes and is considered **not medically necessary**.

III. Hyperthermia in conjunction with isolated limb perfusion/infusion does not improve patient outcomes and is considered **not medically necessary**.

IV. Isolated Limb Perfusion/Infusion has not been medically proven to be effective and is therefore considered **investigational** under the following conditions:
   A. as an adjuvant treatment of surgically treated *recurrent* melanoma with no other evidence of disease; or
   B. as a primary or adjuvant treatment for any other malignant diagnosis (e.g., soft tissue or bone sarcoma).

V. Tumor Necrosis Factor in conjunction with isolated limb perfusion/infusion has not been medically proven to be effective and is therefore considered **investigational**.

POLICY GUIDELINES:

I. Patients typically undergo one treatment with ILP/ILI. Some patients with incomplete responses after the first procedure may undergo a second course of treatment.

II. The Federal Employees Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION:

Isolated Limb Perfusion (ILP) is a surgical procedure in which an artery and vein to an extremity are exposed and cannulated with catheters to circulate blood and drugs. Surgeons occlude the proximal artery and vein and maintain circulation to the limb by using a pump-oxygenator similar to that used for cardiopulmonary bypass in cardiac surgery. Collateral branches of the proximal vein and artery are also ligated and a tourniquet is applied at the root of the extremity to complete the vascular isolation of the limb. Chemotherapeutic drugs are then circulated or perfused for up to 90 minutes and then flushed out of the extremity prior to reestablishing circulation. The major advantage of this procedure is the ability to dose escalate the drugs to levels that cannot be achieved with systemic circulation. The amount of the drug used in ILP would otherwise be toxic if given systemically. The goal of ILP is to effect control of tumor load in an extremity, prevent local recurrences from progressing to unacceptably morbid tumor masses and salvage limbs from amputation.

The primary drug used for perfusion in ILP for extremity melanoma is the nitrogen mustard, melphalan. Melphalan is an alkylating agent with high tissue penetrance that specifically targets melanocytes and melanoma cells. Tumor Necrosis

Factor (TNF) has also been used in conjunction with melphalan as a drug regimen for ILP. Tumor Necrosis Factor is a pleiotropic cytokine produced predominantly by macrophages. Its name was derived from its rapid necrotic effect on bulky subcutaneous tumors in mice. Interferon-gamma is thought to have a synergistic effect on TNF.

The addition of mild hyperthermia (38.5-40.0 degrees C) to ILP is thought to augment the anti-tumor effects of melphalan. The extremity is heated with external warming blankets, and by heating the perfusate solution as it circulates through the pump-oxygenator.

The primary patient population targeted for this regional delivery technique is patients who have unresectable, extensive local recurrent melanoma in the arm or leg whose treatment option would otherwise be limb amputation. Local recurrences are referred to as satellite or in-transit melanoma. ILP has also been utilized as an adjuvant treatment after resection of primary melanoma considered to be at high risk for recurrence or after resection of local recurrences. There has also been extensive research with ILP using melphalan and TNF in locally unresectable sarcomas.

Isolated limb infusion (ILI), a similar, but much less complex technique from isolated limb perfusion, is currently being evaluated in US clinical trials. The ILI technique was developed in the 1990's at the Sydney Melanoma Unit, Sydney Australia and has been investigated as a limb sparing technique for both extremity sarcomas and melanomas. Infusion catheters are placed percutaneously by interventional radiologists without the need for a pump team or cardiopulmonary bypass circuit and require no surgical incision.

RATIONALE:

For select patients with unresectable recurrent melanoma, ILP with melphalan is considered a gold standard of treatment. Parenteral melphalan in isolated limb perfusion is an accepted off-label use. Large case studies have consistently reported impressive complete response rates compared to systemic chemotherapy (complete response rates of 40-60% with an overall response rate of 80%). Historical literature on major limb amputation for recurrent extremity melanoma shows a 5-year survival rate of 12-35%. The poor overall prognosis, morbidity of major limb amputation and the good response rates with ILP are strong arguments against performing amputation of otherwise functional limbs.

In clinical trials investigating ILP with melphalan as an adjuvant treatment in patients with resected primary melanoma considered at high-risk, decrease of local recurrence of the disease occurred, but the overall survival rates remained unchanged.

There is a lack of definitive data proving the benefit of ILP as an adjuvant treatment in patients with recurrent melanoma amenable to surgical resection.

Thus far, clinical trials utilizing the drug regimen of melphalan combined with TNF have found no significant benefit of this drug combination over the use of melphalan alone. TNF is also not a FDA approved drug.

There are no published controlled trials comparing ILP with and without hyperthermia. Published case studies suggest that there is no significant improvement when hyperthermia is used in conjunction with ILP.

Results of a Phase II trial of Isolated Limb *Infusion* (ILI) conducted at Sloan Kettering Cancer Center were published in August 2006 (M Brady, et al). 25 patients with either unresectable melanoma or sarcoma underwent ILI with melphalan and dactinomycin. Outcome data included tumor response at 3 months post ILI. Of the 22 available patients, 11(50%) had a significant response (23% complete response, 27% partial response). Morbidity was considered moderate in most patients. The authors concluded that ILI is well tolerated with promising results. Dr. Brady presented the final report of this Phase II trial at the March 20, 2007 annual meeting of the Society of Surgical Oncology in Washington DC. This phase had enrolled a total of 37 patients with 32 patients evaluable for efficacy and morbidity. 8 patients achieved a complete response and 9 had partial responses, for an overall objective response rate of 53% on an intent-to-treat basis. All the complete responders eventually had disease recurrence after a median of 12 months (range 5-32 months). Among the partial responders, the median time to progression was 11 months. The investigators concluded that the

response rates were comparable to ILP, and morbidity was acceptable and probably less than those associated with ILP, although no head to head comparisons have been done.

CODES:	Number	Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

CPT:	36823	Insertion of arterial and venous cannula(s) for isolated extracorporeal circulation and regional chemotherapy perfusion to an extremity, with or without hyperthermia, with removal of cannula(s) and repair of arteriotomy and venotomy sites
	77600	Hyperthermia, externally generated, superficial (i.e., heating to a depth of 4 cm or less) (**NMN** if used with isolated limb perfusion, CPT 36823)

HCPCS:	J9245	Injection, melphalan HCl, 50 mg
ICD10:	C43.60-C43.62	Malignant melanoma of upper limb, including shoulder (code range)
	C43.70-C43.72	Malignant melanoma of lower limb, including hip (code range)
	C44.601-C44.609 **(E/I)**	Unspecified malignant neoplasm of skin of upper limb, including shoulder (code range)
	C44.611-C44.619 **(E/I)**	Basal cell carcinoma of skin of upper limb, including shoulder (code range)
	C44.621-C44.629 **(E/I)**	Squamous cell carcinoma of skin of upper limb, including shoulder (code range)
	C44.691-C44.699 **(E/I)**	Other specified malignant neoplasm of skin of upper limb, including shoulder (code range)
	C44.701-C44.709 **(E/I)**	Unspecified malignant neoplasm of skin of lower limb, including hip (code range)
	C44.711-C44.719 **(E/I)**	Basal cell carcinoma of skin of lower limb, including hip (code range)
	C44.721-C44.729 **(E/I)**	Squamous cell carcinoma of skin of lower limb, including hip (code range)
	C44.791-C44.799 **(E/I)**	Other specified malignant neoplasm of skin of lower limb, including hip (code range)
	C44.80 **(E/I)**	Unspecified malignant neoplasm of overlapping sites of skin
	C44.81**(E/I)**	Basal cell carcinoma of overlapping sites of skin
	C44.82 **(E/I)**	Squamous cell carcinoma of overlapping sites of skin
	C44.89 **(E/I)**	Other specified malignant neoplasm of overlapping sites of skin

C44.90 **(E/I)**	Unspecified malignant neoplasm of skin, unspecified
C44.91 **(E/I)**	Basal cell carcinoma of skin, unspecified
C44.92 **(E/I)**	Squamous cell carcinoma of skin, unspecified
C44.99 **(E/I)**	Other specified malignant neoplasm of skin, unspecified
C47.10-C47.12 **(E/I)**	Malignant neoplasm of peripheral nerves of upper limb, including shoulder (code range)
C47.20-C47.22 **(E/I)**	Malignant neoplasm of peripheral nerves of lower limb, including hip (code range)
C47.8 **(E/I)**	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C47.9 **(E/I)**	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C49.10-C49.12 **(E/I)**	Malignant neoplasm of connective and soft tissue of upper limb, including shoulder (code range)
C49.20-C49.22 **(E/I)**	Malignant neoplasm of connective and soft tissue of lower limb, including hip (code range)
C49.8 **(E/I)**	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9 **(E/I)**	Malignant neoplasm of connective and soft tissue, unspecified
D03.60-D03.62	Melanoma in situ of upper limb, including shoulder (code range)
D03.70-D03.72	Melanoma in situ of lower limb, including shoulder (code range)

REFERENCES:

*Abe S, et al. Hyperthermic isolated regional perfusion with CDDP for bone and soft tissue sarcoma of the lower limb: pharmacokinetics, thermal dose, toxicity and feasibility. Cancer Chemother Pharmacol 2005 Jul;56(1):55-62.

Alexander HR Jr, et al. Analysis of factors influencing outcome in patients with in-transit malignant melanoma undergoing isolated limb perfusion using modern treatment parameters. J Clin Oncol 2010 Jan 1;28(1):114-8.

Barbour AP, et al. Isolated limb perfusion for malignant melanoma: predictors of response and outcome. Ann Surg Oncol 2009 Dec;16(12):3463-72.

Beasley GM, et al. A phase I study of systemic ADH-1 in combination with melphalan via isolated limb infusion in patients with locally advanced in-transit malignant melanoma. Cancer 2009 Oct 15;115(20):4766-74.

Beasley GM. Prospective multicenter phase II trial of systemic ADH-1 in combination with melphalan via isolated limb infusion in patients with advanced extremity melanoma. J Clin Oncol 2011 Mar 20;29(9):1210-5.

BlueCross BlueShield Association. Isolated limb perfusion/infusion for malignant melanoma. Medical Policy Reference Manual Policy #7.01.12. archived 2011 Feb 10.

Boesch CE, et al. Long-term outcome of hyperthermic isolated limb perfusion (HILP) in the treatment of locoregionally metastasized malignant melanoma of the extremities. Int J Hyperthermia 2010 Feb;26 (1):16-20.

Brady MS, et al. Isolated limb infusion with melphalan and dactinomycin for regional melanoma and soft-tissue sarcoma of the extremity: final report of a phase II clinical trial. Melanoma Res 2009 Apr;19(2):106-11.

Cornett WR, et al. Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosis factor: American College of Surgeons Oncology Group Trial Z0020. J Clin Oncol 2006 Sep 1;24(25):4196-201.

Duprat JP, et al. Long-term response of isolated limb perfusion with hyperthermia and chemotherapy for Merkel cell carcinoma. Eur J Surg Oncol 2009 Jun;35(6):568-72.

Grabellus F, et al. Evaluation of 47 soft tissue sarcoma resection specimens after isolated limb perfusion with TNF-alpha and melphalan: histologically characterized improved margins correlate with absence of recurrences. Ann Surg Oncol 2009 Mar;16(3):676-86.

*Grunhagen DJ, et al. Isolated limb perfusion with tumor necrosis factor and melphalan prevents amputation in patients with multiple sarcomas in arm or leg. Ann Surg Oncol 2005 Jun;12(6):473-9.

Hoven-Gondrie ML, et al. Long-term locoregional vascular morbidity after isolated limb perfusion and external-beam radiotherapy for soft tissue sarcoma of the extremity. Ann Surg Oncol 2007;14(7):2105- 12.

Hoven-Gondrie ML, et al. Isolated limb perfusion and external beam radiotherapy for soft tissue sarcomas of the extremity: long-term effects on normal tissue according to LENT-SOMA scoring system. Ann Surg Oncol 2008 May;15(5):1502-10.

Kroon HM, et al. Outcomes following isolated limb infusion for melanoma. A 14-year experience. Ann Surg Oncol 2008 Nov;15(11):3003-13.

Kroon HM, et al. Isolated limb infusion: A review. J Surg Oncol 2009 Apr 13. [Epub ahead of print].

Lasithiotakis K, et al. Hyperthermic isolated limb perfusion for recurrent melanomas and soft tissue sarcomas: feasibility and reproducibility in a multi-institutional Hellenic collaborative study. Oncol Rep 2010 Apr;23(4):1077-83.

Moncrieff MD, et al. Isolated limb infusion for advanced soft tissue sarcoma of the extremity. Ann Surg Oncol 2008 Oct;15(10):2749-56.

Nachmany I, et al. Efficacy of high vs low dose TNF-isolated limb perfusion for locally advanced soft tissue sarcoma. Eur J Surg Oncol 2009 Feb;35(2):209-14.

National Comprehensive Cancer Network. Clinical practice guideline in oncology. Melanoma 2011 [http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf] accessed 7/6/11.

Raymond AK, et al. Current trends in regional therapy for melanoma: lessons learned form 225 regional chemotherapy treatments between 1995 and 2010 at a single institution. J Am Coll Surg 2011 Apr 12 [Epub ahead of print].

Reintgen M, et al. Regional therapy for recurrent metastatic melanoma confined to the extremity: hyperthermic isolated limb perfusion vs. isolated limb infusion. Cancers 2010 Feb 10;2:43-50.

Sanki A, et al. Isolated limb perfusion and isolated limb infusion for malignant lesions of the extremities. Curr Probl Surg 2011 Jun;48(6):371-430.

Santillan AA, et al. Predictive factors of regional toxicity and serum creatine phosphokinase levels after isolated limb infusion for melanoma: a multi-institutional analysis. Ann Surg Oncol 2009 Sep;16(9):2570-8.

* Key article

KEY WORDS:

Isolated Limb Infusion, Melanoma, Melphalan, Tumor Necrosis Factor, TNF.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based on our review, isolated limb perfusion/infusion is not specifically addressed in National Regional Medicare coverage determinations or policies.