BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Isolated Limb Perfusion/Infusion for Malignant Melanoma

Policy #: 185
Category: Surgery

Latest Review Date: January 2020
Policy Grade: **Effective September 2012: Active Policy but no longer scheduled for regular literature reviews and updates.**

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after July 1, 2005:

Blue Advantage will treat **isolated limb perfusion** with ***melphalan*** as a **covered** benefit when used as a therapeutic treatment of **local recurrence of non-resectable melanoma (i.e., satellite lesions or "in transit" melanoma).**

Blue Advantage will treat **isolated limb perfusion** with ***melphalan*** as a **non-covered** benefit when used for the following indications:

- As an adjuvant treatment of surgically treated primary malignant melanoma with **no clinical evidence of disease** and is a **non-covered** benefit**.**
- As an adjuvant treatment of surgically treated locally recurrent melanoma with **no other evidence of disease** and is considered **investigational**.
- In conjunction with ***tumor necrosis factor or interferon gamma*** for primary malignant melanoma, locally recurrent melanoma with no other evidence of disease or local recurrence of non-resectable melanoma and is considered **investigational**.

Blue Advantage will treat **isolated limb perfusion** in conjunction ***with hyperthermia*** as a **non-covered** benefit and as **investigational**.

Blue Advantage will treat **isolated limb infusion (ILI) with melphalan** as a **covered** benefit for the therapeutic treatment of local recurrence of nonresectable melanoma (i.e., satellite lesions or "in transit" melanoma).

Blue Advantage will treat **isolated limb infusion in the treatment of melanoma for all other indications** as a **non-covered** benefit and as **investigational.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Isolated limb perfusion (ILP) is a method of drug delivery that is designed to deliver high local doses of chemotherapeutic agents to isolated anatomic regions while avoiding systemic toxicity. It has been investigated primarily as a treatment of malignant melanoma arising in the extremities. ILP involves the following steps: 1) mobilization and placement of venotomy and arteriotomy catheters into the major blood vessels (axillary, brachial, iliac, or popliteal artery and vein) proximal to the tumor; 2) isolation of the limb via a tourniquet; and 3) perfusion of a chemotherapeutic drug via an extracorporeal circulation system into the affected extremity. Perfusion lasts for approximately 60 minutes. Melphalan is the drug typically used, but more

recently melphalan has been combined with the cytokine tumor necrosis factor alpha (TNF-alpha) and/or interferon gamma (IFN-gamma).

ILP has also been performed in conjunction with mild hyperthermia based on the theoretical rationale that heat may potentiate the tumor killing effect of melphalan. Hyperthermia is performed by warming the perfusate and by wrapping the treated extremity in a warming blanket. Target tissue temperature is typically 39 to 40 degrees Celsius.

ILP as a treatment for melanoma has been investigated as a treatment of melanoma in these general settings:

1. As adjuvant treatment of surgically treated primary malignant melanoma with no clinical evidence of disease.
2. As adjuvant treatment of surgically treated locally recurrent melanoma with no other evidence of disease.
3. As a therapeutic treatment for local recurrence of non-resectable melanoma (i.e., satellite lesions or "in transit" melanoma).

In isolated limb infusion (ILI), catheters are inserted percutaneously into the axial artery and vein of the affected limb and a pneumatic tourniquet is inflated proximally. Cytotoxic agents are then infused through the arterial catheter and circulated with a syringe for 15 to 20 minutes after which the limb is flushed with a liter of Hartman's solution. Progressive hypoxia occurs, but normothermia is maintained. This procedure differs from ILP primarily by avoiding the use of an extracorporeal circulation system, making it less expensive, requiring fewer medical personnel, and reducing the total operating room time.

KEY POINTS:

Summary of Evidence

Due to the small numbers, inability to blind to treatment assignment, and potentially the lack of good comparators, there may never be a randomized control trial of either ILI or ILP. Large ILP case series have consistently reported impressive complete response rates compared to systemic chemotherapy and there is no alternative therapy that would provide a meaningful comparison.

Except for use of ILI in treatment of local recurrence of nonresectable melanoma, ILI in the treatment of melanoma is considered investigational due to lack of sufficient data concerning outcomes.

Current Clinical Trials and Guidelines

A search of the National Cancer Institute's Physician Data Query database returned no active phase III trials involving isolated limb perfusion and melanoma, as of January 2020.

The National Cancer Comprehensive Cancer Network (NCCN) guidelines for unresectable in-transit melanoma or in-transit recurrence include hyperthermic limb perfusion or infusion with melphalan; these are category 2-B recommendation (meaning the recommendation is based on "lower level evidence' and nonuniform NCCN consensus" without major disagreement).

Physician Specialty Society and Academic Medical Center Input
In response to requests by the Blue Cross Blue Shield Association, responses were received from two academic medical centers while this policy was being reviewed. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement of position statement by the physician specialty societies or academic medical centers, unless otherwise noted. One academic center declined comment, indicating they do not perform this procedure because it is so specialized but instead refer potential candidates (one to two patients per year) to specific center. The reviewer from the second center agreed with the policy conclusions. Citing Cornett et al, the reviewer commented that no data from trials address whether hyperthermia contributes to the effect of ILP with melphalan.

KEY WORDS:
Isolated limb perfusion, ILP, melphalan, malignant melanoma, tumor necrosis factor, interferon gamma, hyperthermia, isolated limb infusion, ILI

APPROVED BY GOVERNING BODIES:
TNF is not FDA approved for any indication
Melphalan is FDA approved

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT codes:	**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
HCPCS:	**Q0083-Q0085**	Chemotherapy administration code range (hospital use only)

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POLICY HISTORY:

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