Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Temsirolimus (Torisel®)	MP-RX-FP-91-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B DRUG

Service Description

This document addresses the use of Temsirolimus (Torisel®), a kinase inhibitor approved by the Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma.

Background Information

Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR). It operates by binding to an intracellular protein known as FKBP-12. This protein-drug complex effectively hinders mTOR's activity, which is responsible for regulating cell division. Inhibition of mTOR activity leads to a halt in the G1 phase of cell growth in treated tumor cells. Additionally, when mTOR is inhibited, its capacity to phosphorylate p70S6k and S6 ribosomal protein, both downstream components of the PI3 kinase/AKT pathway, is disrupted.

Torisel is FDA approved for advanced renal cell carcinoma (RCC). It was approved based on results from a phase 3 trial of patients with previously untreated advanced RCC (clear cell and non-clear cell histologies) (Hudes 2007). Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial renal cell carcinoma diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase >1.5 times the upper limit of normal, more than one metastatic organ site).

The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Torisel. These include its use in relapsed or stage IV RCC for patients who are at poor/intermediate risk as defined by prognostic risk factors used in the previously mentioned study. NCCN also recommends Torisel in certain types of soft tissue sarcoma (PEComa, recurrent angiomyolipoma, and lymphangioleiomyomatosis, rhabdomyosarcoma) and for advanced, recurrent, or metastatic endometrial carcinoma.

Temsirolimus (Torisel®) is considered contraindicated for patients with bilirubin levels exceeding 1.5 xULN. According to the prescribing information, temsirolimus (Torisel) carries the following warnings and precautions:

- Hypersensitivity/infusion reactions, including some rare and potentially life-threatening reactions.
- Hepatic impairment.
- Hyperglycemia and hyperlipidemia.
- Increased susceptibility to infections due to immunosuppression.
- Monitoring for symptoms or radiographic changes indicative of interstitial lung disease (ILD).

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- The potential for bowel perforation.
- Occurrence of renal failure, occasionally fatal.
- Caution during the perioperative period due to abnormal wound healing.
- Risk of proteinuria and nephrotic syndrome.
- Avoidance of live vaccinations and close contact with individuals who have received live vaccines.
- Embryo-fetal toxicity.
- A higher susceptibility of elderly patients to adverse events such as diarrhea, edema, and pneumonia.

The most commonly reported adverse reactions (occurring in ≥ 30% of cases) include rash, asthenia, mucositis, nausea, edema, and anorexia. The most frequent laboratory abnormalities (occurring in ≥ 30% of cases) encompass anemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

Definitions and Measures

- Angiomyolipoma: A neoplasm with perivascular epithelioid cell differentiation (PEComa) often associated with tuberous sclerosis. It is characterized by a mixture of epithelioid cells, smooth muscle, vessels, and mature adipose tissue. The kidney is the most common site of involvement. Other sites of involvement include the liver, lung, lymph nodes, and retroperitoneum. The vast majority of cases follow a benign clinical course. However, cases of metastatic angiomyolipomas with sarcomatoid features have been described.
- Endometrial Adenocarcinoma: An adenocarcinoma arising from the uterine body cavity. This is the most frequent malignant tumor affecting the uterine body, and is linked to estrogen therapy. Most individuals present with uterine bleeding and are over age 40 at the time of diagnosis. The prognosis depends on the stage of the tumor, the depth of the uterine wall invasion, and the histologic subtype. Endometrioid adenocarcinoma is the most frequently seen morphologic variant of endometrial adenocarcinoma (NCI, 2015).
- Karnofsky Performance Status (KPS): A standard way of measuring the ability of individuals with cancer to perform ordinary tasks. The KPS scores range from 0 to 100. A higher score means the person is better able to carry out daily activities. The KPS may be used to determine an individual's prognosis, to measure changes in the ability to function, or to decide if an individual could be included in a clinical trial (NCI, 2015).
- Line of Therapy:
    - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
    - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
    - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- Lymphangioleiomyomatosis: A multifocal neoplasm with perivascular epithelioid cell differentiation (PEComa) affecting almost exclusively females of child-bearing age. It is characterized by the presence of smooth muscle

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and epithelioid cells and by the proliferation of lymphatic vessels. Sites of involvement include the lungs, mediastinum, and the retroperitoneum. It usually presents with chylous pleural effusion or ascites (NCI, 2015).

- Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- One line of therapy: Single line of therapy.
- PEComa: A soft tissue mesenchymal tumor with perivascular epithelioid cell differentiation (PEComa). Representative examples include angiomyolipoma, clear cell-sugar-tumor of the lung, and lymphangioleiomyomatosis.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.
- Unresectable: Unable to be removed with surgery.

Approved Indications

Torisel is approved by the Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma.

Other Uses

See Background section above.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9330	Injection, temsirolimus, 1 mg [Torisel]

ICD-10	Description
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C54.1	Malignant neoplasm of endometrium
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis
C65.1-C65.9	Malignant neoplasm of renal pelvis
D30.00-D30.02	Benign neoplasm of kidney

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D30.10-D30.12	Benign neoplasm of renal pelvis
J84.81	Lymphangioleiomyomatosis
Z85.528	Personal history of other malignant neoplasm of kidney

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Temsirolimus (Torisel®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of advanced Renal Cell Carcinoma and the following are met (Label, NCCN1, 2A):

A. Temsirolimus is used as first-line therapy as a single agent (monotherapy) for (either 1 or 2):

1. Relapsed metastatic disease; **OR**
2. Surgically unresectable stage IV renal carcinoma in individuals with a poor prognosis as manifested by having *at least* three (3) of the following (a through f):
   a. Lactate dehydrogenase greater than 1.5 times the upper limit of normal; **OR**
   b. Hemoglobin less than the lower limit of normal; **OR**
   c. Corrected calcium level greater than 10mg/dL (2.5mmol/liter); **OR**
   d. Interval of less than a year from original diagnosis to the start of systemic therapy; **OR**
   e. Karnofsky performance status less than or equal to 70 or ECOG performance score of 2, 3, or 4; **OR**
   f. Greater than or equal to 2 sites of metastases;

OR

B. Temsirolimus is used for subsequent (second-line) therapy as a single agent (monotherapy) for relapsed metastatic or for surgically unresectable stage IV disease;

OR

ii. Individual has a diagnosis of Soft Tissue Sarcoma and the following are met (NCCN 2A):

A. Temsirolimus is used as a single agent (monotherapy) for sarcoma including, but not limited to, PEComa, recurrent angiomyolipoma, and lymphangioleiomyomatosis; **OR**

B. Temsirolimus is used in combination with cyclophosphamide and vinorelbine for non-pleomorphic rhabdomyosarcoma;

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OR

iii. Individual has a diagnosis of Endometrial Adenocarcinoma or Uterine Perivascular Epithelioid Cell neoplasm (PEComa) and the following are met (NCCN 2A):
   A. Temsirolimus is used as a single agent (monotherapy); **AND**
   B. Individual has unresectable, recurrent, or metastatic disease.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Temsirolimus (Torisel®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of an unacceptable toxicity or disease progression while on the current regimen. The following information should be submitted for reauthorization:
   A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
   B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Bilirubin greater than 1.5 times the upper limit of normal (ULN); **OR**
ii. When the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications

Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

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Drug	Recommended Dosing Schedule
Temsirolimus (Torisel®)	25 mg i.v. once a week
Exceptions	
None	

Reference Information

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: April 7, 2023.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Hudes GR, Carducci MA, Choueiri TK, et al. Temsirolimus, Interferon Alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007; 356:2271-2281.
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
6. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on April 7, 2023
    a. Kidney Cancer. V4.2023. Revised January 18, 2023.
    b. Soft Tissue Sarcoma. V2.2023. Revised April 25, 2023.
    c. Uterine Neoplasms. V2.2023. Revised April 28, 2023.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024

Revised: 11/17/2023