09-J4000-26

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Reviewed: 07/10/24

Revised: 08/15/24

Subject: Tebentafusp-tebn (Kimmtrak®) IV Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Tebentafusp-tebn is a bispecific gp100 peptide-HLA-directed CD3 T cell engager that was approved by the US Food and Drug Administration (FDA) in January 2022 for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. It is the first FDA-approved therapy for uveal melanoma and the first bispecific T-cell engager (BiTE) to receive approval for the treatment of a solid tumor. Tebentafusp was previously granted orphan drug designation for the treatment of uveal melanoma in 2016. In vitro, tebentafusp binds to HLA-A*02:01-positive uveal melanoma cells and activates polyclonal T cells to release inflammatory cytokines and cytolytic proteins, which results in direct lysis of the tumor cells.

Uveal melanoma is a rare subtype of melanoma affecting the eye with an occurrence of about 5 cases per million in the US. It is diagnosed primarily at older ages, with an increase in incidence with age that peaks around an age of 70 years. In a majority of individuals, uveal melanoma develops in the uveal tract (iris, ciliary body, and choroid) of the eye. In choroidal or uveal melanoma, choroidal melanocytes (pigment producing cells in the eye) undergo transformation into cancerous cells. Symptomatic individuals with ocular melanoma may exhibit blurred vision, double vision, irritation, pain, a perception of flashes of light in the eye, a decrease in the total field of vision, and loss of vision. The risk of metastasis in uveal melanoma is dependent upon where along the uveal tract it develops. Iris melanomas have a low rate of metastasis compared to ciliary body and choroidal melanomas. It is estimated that 40 to 50% of individuals with uveal melanoma will develop metastatic disease. Metastasis from ciliary body or choroidal melanoma carries an associated 5-year mortality rate estimated at 30% compared with a rate of 2% to 3% for iris melanoma. The two primary therapeutic options for the treatment of uveal melanomas have been radiation therapy or surgery. The National Comprehensive Cancer Network (NCCN) Guidelines for Melanoma: Uveal (Version 2.2022) list tebentafusp as a category 1 preferred treatment for distant metastatic disease in patients who are HLA A*02:01-positive. However, the guidelines state that when available and clinically appropriate,

enrollment in a clinical trial is recommended as prefer treatment. The guidelines also include a footnote stating that if disease is confined to the liver, regional therapies such as chemoembolization, radioembolization, or immunoembolization should be considered, and that since tebentafusp response rates are low, symptomatic patients may be better palliated by liver-directed treatment first or respond better to ipilimumab/nivolumab.

The safety and efficacy of tebentafusp leading to initial FDA-approval was evaluated in IMCgp100-202, a randomized, open-label, multicenter trial (NCT03070392), The trial enrolled patients with metastatic uveal melanoma (n=378) and were required to be HLA-A*02:01 genotype positive identified by a central assay. Patients were excluded if they received prior systemic therapy for metastatic or advanced uveal melanoma or localized liver-directed therapy. Prior surgical resection of oligometastatic disease was permitted. Patients with clinically significant cardiac disease or the presence of symptomatic or untreated brain metastasis were excluded. Patients were randomized 2:1 to receive tebentafusp weekly by IV infusion administered at 20 mcg IV on Day 1, 30 mcg IV on Day 8, 68 mcg IV on Day 15, and 68 mcg IV once every week thereafter (n=252), or investigator's choice (n=126) of pembrolizumab, ipilimumab, or dacarbazine. Randomization was stratified by lactate dehydrogenase (LDH) level at study entry. Across both arms, patients stopped treatment for disease progression, unless the patient was otherwise deriving benefit, or for unacceptable toxicity. The major efficacy outcome was overall survival (OS). Additional efficacy outcomes were investigator-assessed progression free survival (PFS) and objective response rate (ORR) per RECIST 1.1. The median age was 64 years (range 23 to 92 years); 50% were female, and 87% were White. Baseline ECOG performance status was 0 (73%), 1 (21%), or 2 (0.3%); 36% had elevated LDH level; and 94% had liver metastasis. The efficacy results are summarized in the Table below.

Table 1

	Tebentafusp (n=252)	**Investigator's Choice (pembrolizumab, or ipilimumab, or dacarbazine) (n=126)**
Overall Survival (OS)		
Number of deaths	87 (34.5%)	63 (50%)
Median in months (95% CI)	21.7 (18.6, 28.6)	16 (9.7, 18.4)
HR (95% CI)	0.51 (0.37, 0.71)	
p-value	<0.0001	
Progression-free Survival (PFS)		
Number (%) of patients with event	198 (78.6%)	97 (77%)
Median in months (95% CI)	3.3 (3, 5)	2.9 (2.8, 3)
HR (95% CI)	0.73 (0.58, 0.94)	
p-value	0.0139	
Objective Response Rate (95% CI)	9.1% (5.9, 13.4)	4.8% (1.8, 10.1)
Complete Response	1 (0.4%)	0
Partial Response	22 (8.7%)	6 (4.8%)

The median duration of exposure to tebentafusp was 5.3 months (range: 0.3 to 33 months). Serious adverse reactions occurred in 28% of patients. Serious adverse reactions occurring in ≥2% of patients were cytokine release syndrome (CRS) (10%), rashes (4.5%), pyrexia (2.4%), and hypotension (2%). One patient (0.4%) experienced a fatal adverse reaction (pulmonary embolism). Adverse reactions led to permanent discontinuation in 3.3% of patients. Adverse reactions that led to permanent discontinuation were anaphylactic reaction, brain edema, CRS, fatigue, hepatotoxicity, hypotension, and nausea (each 0.4%). Adverse reactions resulting in dosage interruption occurred in 25% of patients. Adverse reactions

which required dosage interruption in ≥2% of patients included fatigue (3.7%), lipase increased (2.9%), pyrexia (2.4%), ALT increase (2%), and AST increase (2%). Adverse reactions leading to dose reduction occurred in 5% of patients. Adverse reactions which required dosage reduction in ≥2% of patients were CRS (2.4%), and rashes (2%). The most common adverse reactions (≥30%) were CRS, rash, pyrexia, pruritus, fatigue, nausea, chills, abdominal pain, edema, hypotension, dry skin, headache, and vomiting. The most common (≥50%) laboratory abnormalities were decreased lymphocyte count, increased creatinine, increased glucose, increased AST, increased ALT, decreased hemoglobin, and decreased phosphate. Refer to the product labeling for more detailed information on adverse reactions.

POSITION STATEMENT:

Initiation of tebentafusp (Kimmtrak) **meets the definition of medical necessity** when **EITHER** of the following are met ("1" or "2"):

1. Member has a confirmed diagnosis of unresectable or metastatic uveal melanoma, and **ALL** of the following criteria are met ("a", "b", and "c"):
    a. The member is HLA-A*02:01 positive – *supportive medical record documentation or genotyping test results must be submitted*
    b. Tebentafusp will be used as monotherapy (i.e., not used in combination with other chemotherapies or immunotherapies)
    c. Dosage of tebentafusp does not exceed 20 mcg IV on day 1, 30 mcg IV on day 8, 68 mcg IV on day 15, and then 68 mcg IV once weekly
2. Member has another FDA-approved or NCCN-supported diagnosis, and **ALL** of the following criteria are met ("a", "b", and "c"):
    a. **EITHER** of the following ("i" or "ii"):
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert), **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information
        ii. Indication **AND** usage are recognized in the NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    b. Tebentafusp is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis
    c. Dosage of tebentafusp does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Approval duration: 6 months

Continuation of tebentafusp (Kimmtrak) **meets the definition of medical necessity** when **BOTH** of the following criteria are met ("1" and "2"):

1. An authorization or reauthorization for tebentafusp has been previously approved by Florida Blue in the past 2 years for the treatment of unresectable or metastatic uveal melanoma, or another FDA-approved or NCCN-supported diagnosis; **OR** the member has previously met **ALL** indication-specific criteria.
2. **EITHER** of the following based on the member's diagnosis ("a" or "b"):
    a. Unresectable or metastatic uveal melanoma
        i. Tebentafusp will be used as monotherapy (i.e., not used in combination with other chemotherapies or immunotherapies)
        ii. Dosage of tebentafusp does not exceed 68 mcg IV once weekly
        iii. Member has **NOT** experience disease progression during treatment with tebentafusp
    b. Other FDA-approved or NCCN-supported diagnosis, and **ALL** of the following ("i", "ii", and "iii"):
        i. Dosage of tebentafusp does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guideline for the specific diagnosis
        ii. Tebentafusp is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis
        iii. Member has had a beneficial response to treatment with tebentafusp

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma
    - The recommended dosage is 20 mcg IV on Day 1, 30 mcg IV on Day 8, 68 mcg IV on Day 15, and 68 mcg IV once every week thereafter. Treat patients until unacceptable toxicity or disease progression occur.
    - Administer the first three infusions in an appropriate healthcare setting by IV infusion over 15 to 20 minutes. Monitor patients during the infusion and for at least 16 hours after the infusion is complete.
    - If the patient does not experience Grade 2 or worse hypotension (requiring medical intervention) during or after the third infusion, administer subsequent doses in an appropriate ambulatory care setting, and monitor patients for a minimum of 30 minutes following each of these infusions.

Dose Adjustments

- Adverse reactions - No dosage reduction is recommended; however, withholding or discontinuing treatment may be advised. Refer to the product labeling for specific recommendation.
- Hepatic impairment - Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

- Renal impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- Single-dose vial containing 100 mcg of tebentafusp-tebn in 0.5 mL of sterile, preservative-free, clear, colorless or slightly yellowish solution
- Store vials in the original carton refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze. Do not shake.

PRECAUTIONS:

Boxed Warning

- WARNING: CYTOKINE RELEASE SYNDROME

  Cytokine Release Syndrome (CRS), which may be serious or life-threatening, occurred in patients receiving Kimmtrak. Monitor for at least 16 hours following first three infusions and then as clinically indicated.

Contraindications

- None

Precautions/Warnings

- **Cytokine Release Syndrome**: Cytokine release syndrome (CRS), which may be life threatening, occurred in patients receiving tebentafusp. Manifestations of CRS may include fever, hypotension, hypoxia, chills, nausea, vomiting, rash, elevated transaminases, fatigue, and headache. CRS (≥ Grade 2) occurred in 77% of patients in Study IMCgp100-202 who received tebentafusp. Among patients who received tebentafusp, 23% received systemic corticosteroids for at least 1 infusion, 8% received supplemental oxygen during at least 1 infusion, and 0.8% received a vasopressor for at least 1 infusion. CRS led to permanent discontinuation in 1.2% of patients. In Study IMCg100-202, 60% of patients experienced ≥Grade 2 CRS with more than 1 infusion, with the median number of events being 2 (range 1 to 12). The majority (84%) of episodes of CRS started the day of infusion. Among cases that resolved, the median time to resolution of CRS was 2 days. Ensure that healthcare providers administering tebentafusp have immediate access to medications and resuscitative equipment to manage CRS. Ensure patients are euvolemic prior to initiating the infusions. Closely monitor patients for signs or symptoms of CRS following infusions of tebentafusp. Monitor fluid status, vital signs, and oxygenation level and provide appropriate therapy. Withhold or discontinue tebentafusp depending on persistence and severity of CRS.
- **Skin Reactions**: Skin reactions, including rash, pruritus, and cutaneous edema occurred in patients treated with tebentafusp. In study IMCgp100-202, skin reactions occurred in 91% of patients including Grade 2 (44%) and Grade 3 (21%) events. Skin reactions included rash (83%), pruritus (69%), erythema (25%), and cutaneous edema (27%). The median time to onset of skin reactions was 1 day (range: 1 to 55 days). The median time to improvement to ≤Grade 1 was approximately 6 days. Monitor patients for skin reactions. If skin reactions occur, treat with antihistamine and topical or systemic steroids based on persistence and severity of symptoms. Withhold or permanently discontinue tebentafusp depending on the severity of skin reactions.
- **Elevated Liver Enzymes**: In Study IMCgp100-202, increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were observed in 65% of patients treated with tebentafusp. In patients experiencing ALT/AST elevations, 73% initially occurred within the first 3 infusions. Most patients experiencing Grade 3 or 4 ALT/AST elevations had improvement to ≤Grade 1 within 7 days.

For events that were observed outside the setting of CRS, the median time to onset was 129 days. Grade 3 or greater elevations in liver enzymes outside the setting of CRS occurred in approximately 8% of patients. Elevations in liver enzymes led to permanent discontinuation in 0.4% of patients. Monitor ALT, AST, and total blood bilirubin prior to the start of and during treatment with tebentafusp. Withhold tebentafusp according to severity.

- **Embryo-Fetal Toxicity**: Based on the mechanism of action, tebentafusp may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment and for 1 week after the last dose.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9274	Injection, tebentafusp-tebn, 1 microgram

ICD-10 Diagnosis Codes That Support Medical Necessity

C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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4. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 6/26/24.
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6. Nathan P, Hassel JC, Rutkowski P, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. N Engl J Med. 2021;385(13):1196-1206**.**
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 07/10/24.

GUIDELINE UPDATE INFORMATION:

06/15/22	New Medical Coverage Guideline.

07/01/22	Revision: Added HCPCS code C9095.
10/01/22	Revision: Added HCPCS J9274 and deleted codes C9095 and J9999.
08/15/23	Review and revision to guideline consisting of updating the references.
08/15/24	Review and revision to guideline consisting of updating the references.