Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Nogapendekin alfa inbakicept-pmln (Anktiva®)	MP-RX-FP-154-24	☒ 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 Drugs

Service Description

This document addresses the use of Nogapendekin alfa inbakicept-pmln (Anktiva®), an interleukin-15 (IL-15) receptor agonist approved by the Food and Drug Administration (FDA) to be used in combination with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG- unresponsive nonmuscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

Background Information

Bladder cancer affects around 390,000 people and causes 150,000 deaths annually worldwide. In developed regions like North America and Western Europe, most bladder cancers are urothelial. About 70%-80% of new urothelial bladder cancer cases are non-muscle invasive (which is found in the tissue that lines the inner surface of the bladder and hasn't spread into the bladder wall), encompassing Ta (papillary), T1 (submucosal invasive), and Tis (carcinoma in situ [CIS]), which constitute approximately 70%, 20%, and 10% of non-muscle invasive cases, respectively.

Treatment for intermediate or high-risk NMIBC usually involves transurethral resection of the bladder tumor (TURBT) followed by Bacillus Calmette–Guérin (BCG) intravesical therapy. This cancer type has the highest recurrence rate among all cancers, with the majority of patients experiencing a recurrence. Even with optimal treatment, there's a significant risk of recurrence or progression to advanced disease. Specifically, 30% to 40% of NMIBC patients will face recurrence despite adequate BCG treatment, and up to 50% of those who initially respond completely to BCG will eventually relapse. Patients unresponsive to BCG therapy have limited treatment options and require novel interventions.

On April 22, 2024, the FDA approved nogapendekin alfa inbakicept-pmln (Anktiva®) in combination with BCG for adults with BCG-unresponsive NMIBC with CIS, with or without papillary tumors. Nogapendekin alfa inbakicept (NAI), also known as N-803, is an interleukin-15 (IL-15) superagonist fused with an antibody cytokine. Combined with BCG, NAI has shown high efficacy in patients with BCG-unresponsive disease, achieving complete response rates up to 71% in patients with CIS. However, NAI alone has limited effectiveness in treating CIS.

NAI was tested alongside intravesical BCG in the open-label, nonrandomized phase II/III QUILT 3.032 trial. Participants included those without resectable disease post-TURBT and patients with high-grade Ta/T1 disease who had a complete resection before joining the study. Exclusion criteria encompassed a life expectancy under 2 years, inadequate organ function, severe cardiac dysfunction, a history of muscle-invasive, locally advanced,

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metastatic, or extravesical bladder cancer, or any other cancer (except nonmelanoma skin cancer) within the past 5 years. The primary efficacy outcomes were complete response (CR) at any time and the duration of complete response (DOR), defined by negative cystoscopy (with TURBT/biopsies as needed) and urine cytology.

The study had three patient cohorts: Cohort A included patients with bladder CIS with or without Ta/T1 papillary disease; Cohort B included patients with high-grade papillary Ta/T1 only disease, treated with NAI plus BCG; and Cohort C included patients with bladder CIS, with or without Ta/T1 papillary disease, that were treated with NAI alone. At a median follow-up of 24 months 71% (58 of 82 evaluable patients) patients with bladder CIS (Cohort A) achieved a complete response, with a median response duration of 26.6 months. Only five patients (9%) underwent radical cystectomy. The two-year disease-specific survival (DSS), progression-free survival (PFS), and overall survival (OS) for all patients with CIS were 100%, 85%, and 94%, respectively.

The median follow up time in the cohort of patients with high-grade papillary Ta/T1 only disease that were treated with NAI plus BCG (Cohort 2) was 20.7 months. In this cohort, 55.4% of the 72 patients achieved disease-free survival (DFS) at 12 months, and a median DFS of 19.3 months. At a median follow-up of 21 months, the two-year DFS, DSS, PFS, and OS were 48%, 98%, 89%, and 92%, respectively. Only five patients (7%) underwent radical cystectomy.

Only 2 out of 10 patients with bladder CIS, with or without Ta/T1 papillary disease, who were treated with NAI alone achieved a complete response after 3 months, leading to the discontinuation of this cohort about 6 months into the study due to lack of efficacy.

The most frequent grade 3 treatment-related adverse events included hematuria and urinary tract infections (2% each), dysuria, and pollakiuria (1% each). Treatment-related adverse events requiring hospitalization occurred in 15% of cases, with about 5% being bladder-related, including hematuria (2%).

The recommended dose of nogapendekin alfa inbakicept-pmln is 400 mcg, administered intravesically with BCG once a week for 6 weeks as induction therapy. If CR is not achieved at month 3, a second induction course may be given. For maintenance after induction therapy, the dose is 400 mcg with BCG once a week for 3 weeks at months 4, 7, 10, 13, and 19 (for a total of 15 doses). For patients with an ongoing CR at month 25 or later, maintenance instillations with BCG can be given once a week for 3 weeks at months 25, 31, and 37 for up to 9 additional instillations. Treatment should be discontinued if disease persists after the second induction, if there is recurrence or progression of the disease, or if there is unacceptable toxicity. The maximum treatment duration is 37 months.

<u>Definitions</u>

- Carcinoma in situ (CIS): This refers to a flat, high-grade lesion confined to the bladder lining.
- Non-Muscle Invasive Bladder Cancer (NMIBC) with CIS: Involves flat, high-grade lesions (CIS) that are confined to the bladder lining. CIS is always high-grade and can be present with or without concurrent Ta/T1 papillary tumors.
- BCG: Bacillus Calmette-Guerin

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- BCG unresponsive: Defined as persistent disease following adequate BCG therapy [≥5 of 6 induction doses plus ≥2 doses of maintenance or of 2nd induction], disease recurrence after an initial tumor-free state following adequate BCG therapy, or Ta/T1 disease following a single induction course of BCG.

Approved Indications

Nogapendekin alfa inbakicept-pmln (Anktiva®) is indicated by the FDA to be used with Bacillus Calmette-Guérin (BCG) for the treatment of adult patients with BCG- unresponsive nonmuscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

Other Uses

None

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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
J9999	Not otherwise classified, antineoplastic drugs

ICD-10	Description
C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder
C67.4	Malignant neoplasm of posterior wall of bladder
C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder
C67.9	Malignant neoplasm of bladder, unspecified
D09.0	Carcinoma in situ of bladder
Z85.5	Personal history of malignant neoplasm of urinary tract

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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.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Nogapendekin alfa inbakicept-pmln (Anktiva®)

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. The patient has a diagnosis of nonmuscle invasive bladder cancer (NMIBC) (Label, NCCN 2A)**; AND**
ii. The patient has carcinoma in situ (CIS) with or without papillary tumors; **AND**
iii. The patient's cancer is BCG- unresponsive**; AND**
iv. The patient is using in combination with BCG; **AND**
    A. The patient is using as a first induction cycle**;**
    OR
    B. The patient is using as second induction cycle; **AND**
        1. It has been at least three months since previous induction cycle; **AND**
        2. There is evidence that complete response was not achieve at month three after initial induction cycle
    OR
    C. The patient is using as maintenance therapy at either 4, 7, 10, 13 and 19 months after induction cycle(s);
    OR
    D. The patient is using as maintenance therapy at either 25, 31, and 37 month after induction cycle(s); **AND**
        1. It is documented that the patient has experienced ongoing complete response at month 25 and later.

B. **Criteria For Continuation of Therapy**

i. MMM considers continuation of Nogapendekin alfa inbakicept-pmln (Anktiva®) 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 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.

ii. Reauthorization of Nogapendekin alfa inbakicept-pmln (Anktiva®) will be considered medically necessary in the following scenarios:
A. Administration of a second induction cycle when there is evidence that complete response was not achieved at month 3.
B. Maintenance treatment at months 4, 7, 10, 13 and 19.
C. For patients with evidence of ongoing complete response at month 25 and later, additional maintenance instillations with BCG may be administered once a week for 3 weeks at months 25, 31, and 37.

iii. The recommended duration of treatment is until disease persistence after second induction, disease recurrence or progression, unacceptable toxicity, or a maximum of 37 months.

C. **Authorization Duration**
i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months (maximum duration of therapy is 37 months)

D. **Conditions Not Covered**

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

Nogapendekin alfa inbakicept-pmln (Anktiva®) may not be approved when the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

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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.

Drug	Recommended Dosing Schedule	Quantity Limitations
Nogapendekin alfa inbakicept-pmln (Anktiva®)	• For induction: 400 mcg administered intravesically with BCG once a week for 6 weeks. A second induction course may be administered if complete response is not achieved at month 3. • For maintenance: 400 mcg administered intravesically with BCG once a week for 3 weeks at months 4, 7, 10, 13 and 19. For patients with an ongoing complete response at month 25 and later, additional maintenance instillations with BCG may be administered once a week for 3 weeks at months 25, 31, and 37.	• Induction: One 400 mcg/4mL single dose vial per week, up to a maximum of 6 vials per induction cycle (for a maximum of two induction cycles at least three months apart) • Maintenance: One 400 mcg/4mL single dose vial per week, up to a maximum of 3 vials per maintenance cycle.
Exceptions		
None		

Reference Information

- Anktiva [package insert]. Culver City, CA; Altor BioSciences, LLC; April 2024. Accessed April 2024.
- Black P. Treatment of recurrent or persistent non-muscle invasive urothelial carcinoma of the bladder. Topic last updated June 13, 2024. Available at: https://www.uptodate.com/contents/treatment-of-recurrent-or-persistent-non-muscle-invasive-urothelial-carcinoma-of-the-bladder?search=non-muscle%20invasive%20urothelial%20bladder%20cancer%20unresponsive%20to%20BCG&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2#H3121780479
- FDA Resources for Information | Approved Drugs. FDA approves nogapendekin alfa inbakicept-pmln for BCG-unresponsive non-muscle invasive bladder cancer. April 22, 2024. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nogapendekin-alfa-inbakicept-pmln-bcg-unresponsive-non-muscle-invasive-bladder-cance
- Karim Chamie et al. Final clinical results of pivotal trial of IL-15RαFc super-agonist N-803 with BCG in BCG-unresponsive CIS and papillary non-muscle-invasive bladder cancer (NMIBC). JCO 40, 4508-4508(2022). DOI:10.1200/JCO.2022.40.16_suppl.4508. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38320011
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Bladder Cancer. Version 4.2024 — May 9, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception	New Medical Policy creation	7/29/2024	8/7/2024

Revised: 07/01/2024