Drug Policy:

Bevacizumab Products

POLICY NUMBER UM ONC_1028	**SUBJECT** Bevacizumab Products: Avastin™ (bevacizumab)/ Mvasi™(bevacizumab-awwb)/Zirabev™ (bevacizumab-bvzr) Alymsys™ (bevacizumab-maly)/Vegzelma (bevacizumab-adcd)		**DEPT/PROGRAM** UM Dept	**PAGE 1 of 6**
DATES COMMITTEE REVIEWED 11/04/10, 10/05/11, 02/08/12, 10/13/13, 12/03/14, 01/19/15, 04/13/16, 02/06/17, 10/11/17, 09/21/18, 07/10/19, 09/11/19, 12/11/19, 01/08/20, 02/12/20, 03/11/20, 07/08/20, 07/14/21, 10/13/21, 11/15/21, 12/08/21, 01/12/22, 03/09/22, 05/11/22, 06/08/22, 07/13/22, 09/14/22, 11/09/22, 12/14/22, 03/08/23	**APPROVAL DATE** March 8, 2023	**EFFECTIVE DATE** March 31, 2023	**COMMITTEE APPROVAL DATES** 11/04/10, 10/05/11, 02/08/12, 10/13/13, 12/03/14, 01/19/15, 04/13/16, 02/06/17, 10/11/17, 09/21/18, 07/10/19, 09/11/19, 12/11/19, 01/08/20, 02/12/20, 03/11/20, 07/08/20, 07/14/21, 10/13/21, 11/15/21, 12/08/21, 01/12/22, 03/09/22, 05/11/22, 06/08/22, 07/13/22, 09/14/22, 11/09/22, 12/14/22, 03/08/23	
PRIMARY BUSINESS OWNER: UM		**COMMITTEE/BOARD APPROVAL** Utilization Management Committee		
URAC STANDARDS HUM v8: UM 1-2; UM 2-1	**NCQA STANDARDS** UM 2		**ADDITIONAL AREAS OF IMPACT**	
CMS REQUIREMENTS	**STATE/FEDERAL REQUIREMENTS**		**APPLICABLE LINES OF BUSINESS** Commercial, Exchange, Medicaid	

I. PURPOSE

To define and describe the accepted indications for Bevacizumab Products: Avastin (bevacizumab)/ Mvasi (bevacizumab-awwb)/Zirabev (bevacizumab-bvzr)/Alymsys (bevacizumab-maly)/Vegzelma (bevacizumab-adcd) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

New Century Health (NCH) is responsible for processing all medication requests from network ordering providers. Medications not authorized by NCH may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

II. INDICATIONS FOR USE/INCLUSION CRITERIA

A. Continuation requests for a not-approvable medication shall be exempt from this NCH policy provided:

1. The requested medication was used within the last year, AND
2. The member has not experienced disease progression and/or no intolerance to the requested medication, AND
3. Additional medication(s) are not being added to the continuation request.

B. Brain Necrosis

1. Avastin (bevacizumab)/bevacizumab biosimilars may be used as monotherapy for members with brain necrosis or edema due to cranial irradiation. Use of Avastin (bevacizumab)/bevacizumab biosimilar is not recommended in members with intracranial hemorrhage.

C. Cervical Cancer

1. For members with metastatic/recurrent/unresectable cervical cancer with tumor PD-L1 staining showing a CPS of less than 1%, Avastin (bevacizumab)/bevacizumab biosimilar may be used as first line/initial therapy in any one of the following regimens:
   a. Avastin (bevacizumab)/bevacizumab biosimilar + cisplatin/carboplatin + paclitaxel
   b. Avastin (bevacizumab)/bevacizumab biosimilar + topotecan + paclitaxel
2. NOTE: Per NCH policy, [Avastin (bevacizumab)/bevacizumab biosimilar + Keytruda (pembrolizumab) + cisplatin/carboplatin + paclitaxel] is Not Approved for initial treatment of PD-L1 positive (PD-L1 greater than or equal to 1%) metastatic cervical cancer. The above policy position is based on the results of KEYNOTE-826 trial referenced below. This trial showed no overall survival benefit from adding bevacizumab to [platinum + paclitaxel + pembrolizumab] in PD-L1 positive patients with metastatic/recurrent/inoperable cervical carcinoma. Please refer to the NCH recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.

D. Colorectal Cancer

1. The member has unresectable advanced or metastatic colorectal cancer and Avastin (bevacizumab)/bevacizumab biosimilar is being used as ONE of the following:
   c. As initial therapy in combination with capecitabine or with FOLFOX, FOLFIRI, FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin), 5-FU/LV (fluorouracil and leucovorin), or CapeOX (capecitabine and oxaliplatin).
   d. As subsequent line of therapy given in combination with FOLFOX, FOLFIRI, XELIRI, and XELOX/CapeOX.
   e. Avastin (Bevacizumab/bevacizumab biosimilar may be used for up to 2 lines of therapy in the metastatic setting or up to 3 lines of therapy for Avastin (bevacizumab)/bevacizumab biosimilar + Lonsurf (trifluridine and tipiracil).

E. Glioblastoma

1. The member has glioblastoma, anaplastic astrocytoma, or high-grade glioma and Avastin (bevacizumab)/bevacizumab biosimilar is being used as a single agent OR
2. Avastin (bevacizumab)/bevacizumab biosimilar may be used in combination with irinotecan, carboplatin, carmustine, lomustine, or temozolomide for recurrent glioblastoma, anaplastic astrocytoma, or high-grade glioma.

F. Hepatocellular Carcinoma

1. Member has metastatic/inoperable/advanced hepatocellular carcinoma (Child-Pugh Class A only) and Avastin (bevacizumab)/bevacizumab biosimilar will be used in combination with Tecentriq (atezolizumab) for initial therapy.

G. Non-Small Cell Lung Cancer (NSCLC)

1. Avastin (bevacizumab)/bevacizumab biosimilar- based regimens are Not Approvable for metastatic Non-Small Cell Lung Cancer with the following exception:
    a. For first/initial line therapy for members with recurrent/metastatic non-squamous Non-Small Cell Lung Cancer as a part of [carboplatin + paclitaxel + bevacizumab + atezolizumab] followed by maintenance atezolizumab ± bevacizumab; the above regimen is Not Approvable if member has experienced disease progression on prior Immune Checkpoint Inhibitor therapy.
2. NOTE: Per NCH Policy, regimens containing [Avastin (bevacizumab)/bevacizumab biosimilar + platinum-based chemotherapy] are Not Approvable for all lines of therapy with the exception noted above in Section G-1(a). This Policy Position is based on:
    b. Lack of data supporting the use of such regimens in 2nd line or later lines of therapy, and
    c. Increased risk of serious adverse effects, and
    d. Marginal PFS and OS benefit in the first line setting as shown in randomized trials (e.g., a 2 month OS benefit and a 1.3 month PFS benefit with 15 treatment related deaths in the bevacizumab arm including 5 from pulmonary hemorrhage, please see reference).
    e. Alternative agents/regimens recommended by NCH can be found at: http://pathways.newcenturyhealth.com.
3. NOTE: Per NCH Policy, [Avastin(bevacizumab)/bevacizumab biosimilar + Tarceva (erlotinib)] is Not Approvable for the treatment of metastatic Non-Small Cell Lung Cancer. The above Policy Position is based on the lack of Level 1 evidence (randomized trials and or meta-analyses) to show superior outcomes with the above regimen compared to NCH recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.

H. Ovarian Cancer

1. The member has recurrent or metastatic ovarian cancer and Avastin (bevacizumab)/bevacizumab biosimilar may be used in any of the following clinical settings:
    a. For initial/first line therapy of stage II- IV, Avastin (bevacizumab)/bevacizumab biosimilar may be used with chemotherapy.
    b. Avastin (bevacizumab)/bevacizumab biosimilar may be used for maintenance therapy after complete/partial response to primary chemotherapy + bevacizumab, for stage II-IV disease as follows:
        i. As monotherapy for BRCA 1 or 2 Wild-Type or Unknown, HRD negative (Homologous Recombination Deficiency negative) or HRD unknown OR
        ii. In combination with Lynparza (olaparib) for BRCA 1 or 2 mutation (germline or somatic) or HRD positive.
2. For therapy of relapsed/recurrent ovarian cancer, Avastin (bevacizumab)/bevacizumab biosimilar may be used as monotherapy or with chemotherapy.

I. Renal Cell Carcinoma

1. The member has recurrent or metastatic disease and Avastin (bevacizumab)/bevacizumab biosimilar is being used as a single agent for members who have experienced disease

progression on an oral TKI (e.g., pazopanib) AND an Immune Checkpoint Inhibitor (e.g., pembrolizumab).

III. EXCLUSION CRITERIA

A. Avastin (bevacizumab)/bevacizumab biosimilar is being used on or after disease progression on a bevacizumab containing regimen; except in colorectal cancer, bevacizumab may be used up to 2 lines of therapy in the metastatic setting or up to 3 lines of therapy for bevacizumab + Lonsurf (trifluridine and tipiracil).

B. Members with Child-Pugh Class B or C hepatocellular carcinoma.

C. Dosing exceeds single dose limit of bevacizumab/bevacizumab biosimilar 15 mg/kg. Per NCH Policy, the maximum dose of Avastin (bevacizumab)/bevacizumab biosimilar when used in combination with irinotecan/FOLFIRI/FOLOX/IROX regimen is 5 mg/kg.

D. For Brain Necrosis: Treatment exceeds the maximum duration limit of 4 doses (dose range from 5 mg/kg every 2 weeks to 7.5 mg/kg every 3 weeks).

E. Investigational use of bevacizumab products with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:

1. Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
2. Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
4. Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
5. That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
6. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
7. That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

IV. MEDICATION MANAGEMENT

A. Please refer to the FDA label/package insert for details regarding these topics.

V. APPROVAL AUTHORITY

A. Review – Utilization Management Department

B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

A. None

VII. REFERENCES

A. Sandler A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006 Dec 14;355(24):2542-50.

B. Socinski MA, et al. IMpower150 Clinical Trial. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med. 2018 Jun 14;378(24):2288-2301.

C. Barlesi F, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol 2013; 31:3004.

D. Pfeiffer P, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. Lancet Oncol. 2020 Mar;21(3):412-420.

E. Yang JC, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med. 2003 Jul 31;349(5):427-34.

F. Colombo N, et al. KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med. 2021 Nov 11;385(20):1856-1867.

G. Tewari KS, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014 Feb 20;370(8):734-43.

H. Finn RS, et al. IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894-1905.

I. Suh YJ, et al. Bevacizumab versus PARP-inhibitors in women with newly diagnosed ovarian cancer: a network meta-analysis. BMC Cancer. 2022 Mar 30;22(1):346.

J. Ray-Coquard I, et al. PAOLA-1 Clinical Trial. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2416-2428.

K. Tewari KS, et al. Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer. J Clin Oncol. 2019 Sep 10;37(26):2317-2328.

L. Burger RA. et al. Independent radiologic review of the Gynecologic Oncology Group Study 0218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer. Gynecol Oncol. 2013 Oct;131(1):21-6.

M. Oza AM, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol. 2015 Aug;16(8):928-36.

N. Aghajanian C, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 Jun 10;30(17):2039-45.

O. Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015;139(1):10–16.

P. Coleman RL, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(6):779–791.

Q. Pujade-Lauraine E, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014 May 1;32(13):1302-8.

R. Avastin Product Information. Genentech, Inc. South San Francisco, CA 2021.

S. Mvasi Product Information. Amgen, Inc. Thousand Oaks, CA 2021.

T. Zirabev Product Information. Pfizer, Laboratories Div Pfizer Inc NY, NY 2022.

U. Vegzelma Product Information. Celltrion USA Inc. Sunnyvale, CA 2022

V. Clinical Pharmacology Elsevier Gold Standard 2023.

W. Micromedex Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2023.

X. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2023.

Y. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2023.

Z. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.

AA. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.

BB. NCQA UM 2023 Standards and Elements.