CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Cetuximab (Erbitux®)

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NantHealth® | Eviti®

Please note the following:

Cetuximab (Erbitux®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Cetuximab (Erbitux): Discussion

Cetuximab is a recombinant chimeric human/mouse IgG1 monoclonal antibody that binds to epidermal growth factor receptor (EGFR) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands. Epidermal growth factor (EGF) is a protein that stimulates cell growth and differentiation by binding to its receptor, EGFR. Epidermal growth factor receptor (EGFR) is a signaling pathway that regulates cell differentiation, proliferation, migration, angiogenesis, and apoptosis and is a member of the ErbB family of receptors. EGFR subtypes include, but may not be limited to, exon 19 deletion (19del), exon 21 L858R, S7681, L861Q, T790M, G718A, LL861, and G719X. The EGFR signaling pathway regulates cell differentiation, proliferation, migration, angiogenesis, and apoptosis, all of which become deregulated in cancer cells. Cetuximab binds to EGFR with high specificity and a higher affinity than either epidermal growth factor or transforming growth factor-alpha (TGF-alpha), thus blocking the ligand-induced phosphorylation of EGFR.[1]

Cetuximab is approved by the Food and Drug Administration (FDA) for head and neck cancer (squamous cell), metastatic colorectal cancer (KRAS wild-type), and metastatic colorectal cancer that is BRAF V600E mutation positive. Wild-type is the natural, unchanged (unmutated) form of the gene, as in KRAS and NRAS wild-type, and BRAF wild-type. [2]

The Mitogen-Activated Protein Kinase (MAPK) is a pathway that involves 3 series of protein kinase cascades, which play a critical role in the regulation of cell proliferation. MAPK pathway of RAS/RAF/MEK/ERK is downstream of EGFR; mutations in components of this pathway are now established to be strong negative predictive markers, essentially precluding the efficacy of these. Patients with known KRAS or NRAS-mutant tumors in colon and rectal cancers should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have a minimum chance of benefit. Cetuximab or panitumumab should only be used for left-sided tumors in colon cancer. The panel defines the left side of the colon as splenic flexure to the rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through the cecum) are unlikely to respond to cetuximab and panitumumab.[3]

Cetuximab can cause serious and fatal infusion reactions. Cardiopulmonary arrest or sudden death occurred in patients with squamous cell carcinoma of the head and neck receiving cetuximab with radiation therapy or with a cetuximab product with platinum-based therapy and fluorouracil.[2]

The National Comprehensive Cancer Network (NCCN) endorses cetuximab in the following cancer types: colon, head and neck, lung (non-small cell), penile, rectal, and squamous cell of the skin. [3,4,5,6,7,8.]

Cetuximab: Definitions

- **BRAF gene -** A gene that encodes a protein belonging to the RAF family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion.
- **BRAF V600E mutation positive –** A mutation that accounts for 8–10% of metastatic colorectal cancer (mCRC) patients and is an established poor prognostic factor.
- **Deficient mismatch repair/microsatellite instability high (dMMR/MSI-H)** -When the microsatellite DNA segments in cancer cells show changes (mutations), this indicates that the tumor cells are deficient in the repair of the mismatch errors. These cancers have microsatellite instability (also called MSI-High, MSI-H, or mismatch repair deficiency, dMMR).
- **Food and Drug Administration (FDA)** – The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Human papillomavirus (HPV) –** The most common sexually transmitted infection. HPV is usually harmless and goes away by itself, but some types can lead to cancer.
- **KRAS gene** - A gene that makes a protein that is involved in cell signaling pathways that control cell growth, cell maturation, and cell death.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of 32 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards

are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

- **NRAS gene –** A gene that provides instructions for making a protein called N-Ras that is involved primarily in regulating cell division.
- **Proficient mismatch repair/microsatellite-stable (pMMR/MMS) –** When microsatellite DNA segments are unchanged (not mutated), the tumor cells are considered microsatellite stable (MSS) or have proficient mismatch repair. MSS cancers have normal levels of mismatch repair gene and protein expression and are able to correct DNA mismatch repair errors proficiently.
- **p16-negative** – p16 is a tumor suppressor protein that plays a role in cell cycle regulation. Loss of p16 expression by deletion, mutation, or hypermethylation is common in squamous cell head and neck cancer and is associated with a worse prognosis.
- **p16 (HPV)-positive** – p16 expression (p16 positive) has been correlated with improved outcomes.
- **T790M negative mutation –** Absence of most common resistance mutation after treatment with EGFR tyrosine kinase inhibitors (TKIs).
- **T790M positive mutation** – The most commonly found mutation in non-small cell lung cancer that has a TKI-sensitive EGFR mutation and has developed resistance after TKI treatment.
- **Transforming growth factor-alpha (TGF-alpha)** – A transforming growth factor that is a ligand for the epidermal growth factor receptor, which activates a signaling pathway for cell proliferation, differentiation, and development.

Cetuximab: Policy

Cetuximab will be considered for coverage when the following criteria are met:

Colon Cancer (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy for KRAS/NRAS/BRAF wild-type and left-sided only tumors in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CapeOx (capecitabine and oxaliplatin), OR FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if intensive therapy is recommended for one of the following:
   a) Adjuvant treatment following synchronized or staged resection and/or local therapy for synchronous liver and/or lung metastases that converted from unresectable to resectable disease after primary treatment for proficient mismatch repair/microsatellite-stable (pMMR/MMS) or ineligible for, OR progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability-high (dMMR/MSI-H)

b) Adjuvant treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy for pMMR/MMS, or ineligible for, or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H
c) Adjuvant treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy for dMMR/MSI-H
d) Adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after initial treatment for pMMR/MMS, or ineligible for or progression on a checkpoint inhibitor immunotherapy for dMMR/MSI-H; OR

4. Adjuvant treatment in combination with irinotecan for unresectable metachronous metastases (KRAS/NRAS/BRAF wild-type and left-sided only tumors only) for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability-high (dMMR/MSI-H) that converted to resectable disease after initial treatment; OR
5. Adjuvant treatment in combination with encorafenib for unresectable metachronous metastases (BRAF V600E mutation-positive) for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability-high (dMMR/MSI-H) that converted to resectable disease after initial treatment; OR
6. Therapy for KRAS/NRAS/BRAF wild-type and left-sided only tumors as a single agent if intensive therapy not recommended as one of the following:
   a) Adjuvant treatment following synchronized or staged resection and/or local therapy for synchronous liver and/or lung metastases that converted from unresectable to resectable disease after primary treatment for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability-high (dMMR/MSI-H)
   b) Adjuvant treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy for pMMR/MMS, or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H
   c) Adjuvant treatment following resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy for dMMR/MSI-H
   d) Adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after initial treatment for pMMR/MMS, or ineligible for, or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H; OR

Note: Biologic therapy is only appropriate for continuation of a favorable response from conversion therapy.

7. Therapy for KRAS/NRAS/BRAF wild-type gene and left-sided only tumors in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CapeOx (capecitabine and oxaliplatin), or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for proficient mismatch repair/microsatellite-stable (pMMR/MMS), OR ineligible for OR progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability-high (dMMR/MSI-H) if intensive therapy is recommended for one of the following:
   a) Primary treatment for locally unresectable or medically inoperable disease
   b) Primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with existing or imminent obstruction
   c) Synchronous unresectable metastases of other sites

d) Initial treatment for unresectable metachronous metastases in patients who have not received previous therapy with FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy
e) Progression on non-intensive therapy, unless prior fluoropyrimidine received, with improvement in functional status; OR

8. Primary treatment for unresectable synchronous liver and/or lung metastases (KRAS/NRAS/BRAF wild-type gene and left-sided only tumors) in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) and patient is not a candidate for immunotherapy; OR
9. Initial treatment for unresectable metachronous metastases (KRAS/NRAS/BRAF wild-type gene and left-sided tumors only) in combination with irinotecan, or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) and patient is not a candidate for immunotherapy and received previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
10. Initial treatment in combination with encorafenib for unresectable metachronous metastases (BRAF V600E mutation positive) for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) and patient is not a candidate for immunotherapy and has received previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
11. Therapy for KRAS/NRAS/BRAF wild-type gene and left-sided only tumors for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) as a single agent if intensive therapy is not recommended for one of the following:
    a) Primary treatment for locally unresectable or medically inoperable disease
    b) Primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with existing or imminent obstruction
    c) For synchronous unresectable metastases of other sites
    d) Initial treatment for unresectable metachronous metastases in patients who have not received previous therapy with FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy; OR
12. Subsequent therapy for progression of advanced or metastatic disease (KRAS/NRAS/BRAF wild-type and left-sided tumors only) for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) in combination with one of the following:
    a) Irinotecan, FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen, or as a single agent for patients who cannot tolerate irinotecan, if previously treated with

b) Irinotecan, FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CapeOX (capecitabine and oxaliplatin), or as a single agent for patients who cannot tolerate irinotecan, if previously treated with irinotecan-based therapy without oxaliplatin
c) Irinotecan or as a single agent for patients who cannot tolerate irinotecan if previously treated with oxaliplatin and irinotecan
d) Irinotecan or as a single agent for patients who cannot tolerate irinotecan if previously treated without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab; OR

13. Subsequent therapy in combination with encorafenib for progression of advanced or metastatic disease (BRAF V600E mutation-positive) for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability-high (dMMR/MSI-H) in patients previously treated with one of the following:
    a) Oxaliplatin-based therapy without irinotecan
    b) Irinotecan-based therapy without oxaliplatin
    c) With irinotecan and oxaliplatin
    d) Without irinotecan or oxaliplatin
    d) Without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab [3]

Note: The patient should not have received prior treatment with cetuximab or panitumumab.

Head and Neck Cancers

Cancer of the Glottic Larynx (Squamous Cell)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Primary concurrent systemic therapy/radiation as a single agent for one of the following:
    a) T3, N0-3 disease requiring (amenable to) total laryngectomy
    b) Selected T4a patients who decline surgery; OR
4. Sequential systemic therapy/radiation as a single agent given weekly following a partial response at the primary site to induction chemotherapy for one of the following:
    a) T3, N0-3 disease requiring (amenable to) total laryngectomy
    b) Selected T4a patients who decline surgery, OR
5. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin-ineligible with extranodal extension for one of the following:
    a) T1-2, N0 or select T3, N0 disease amenable to larynx-preserving (conservation) surgery
    b) Positive margin for T3, N0-3 disease requiring (amenable to) total laryngectomy
    c) Positive margin for T3, N0-3 disease following laryngectomy and less than partial response at the primary site to induction chemotherapy
    d) Positive margin for T4a, N0-3 disease

Cancer of the Hypopharynx (Squamous Cell)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Primary concurrent systemic therapy/radiation as a single agent for one of the following:
   a) T1, N+ disease
   b) T2-3, N0-3 disease requiring (amenable to) pharyngectomy with partial or total laryngectomy;
4. Sequential systemic therapy/radiation as a single agent given weekly for T1, N+, or T2-3, N0-3 disease requiring (amenable to) pharyngectomy with partial or total laryngectomy, or for T4a, N0-3 disease for one of the following:
   a) Partial response at the primary site and stable or improved disease in the neck after induction chemotherapy
   b) Complete response at the primary site and stable or improved disease in the neck after induction chemotherapy; OR
5. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin-ineligible for one of the following:
   a) With extranodal extension with or without positive margin for most T1, N0, or selected T2, N0 tumors amenable to larynx-preserving (conservation) surgery
   b) Positive margin T2, N0 tumors amenable to larynx-preserving (conservation) surgery; OR
6. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin-ineligible and extranodal extension and/or positive margin for one of the following:
   a) T1, N+ or T2-3, N0-3 disease requiring (amenable to) pharyngectomy with partial or total laryngectomy
   b) T1, N+ or T2-3, N0-3 disease with partial response and stable or improved disease in the neck or less than partial response at the primary site following induction chemotherapy
   c) T4a, N0-3 disease
   d) T4a, N0-3 disease with less than partial response at the primary site following induction chemotherapy

Cancer of the Nasopharynx (Squamous Cell)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-line or subsequent-line systemic therapy (if not previously used) in combination with carboplatin for T1-4, N0-3, M1 for one of the following:
   a) Oligometastatic disease and performance status (PS) 0-2
   b) Widely metastatic disease and good PS 0-2

Note: If complete response (CR) or near CR, consider continued systemic therapy.

Cancer of the Oral Cavity (Including Mucosal Lip and Squamous Cell)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

3. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin-ineligible for one of the following:
   a) Extranodal extension with or without positive margin for T1-3, N0-3; or T4a, N0-3 disease
   b) Positive margins for T3, N0; T1-3, N1-3; or T4a, N0-3 disease
   c) Positive margins for T1-2, N0 disease: OR
4. Primary concurrent systemic therapy/radiation as a single agent for selected patients who decline or are unfit for surgery with all of the following:
   a) At least 18 years of age; AND
   b) Prescribed or in consultation with an oncologist; AND
   c) Primary concurrent systemic therapy/radiation as a single agent for p16-negative for one of the following:
      i. T1-2, N1 disease
      ii. T3-4a, N0-1 disease
      iii. T1-4a, N2-3 disease; OR
5. Primary concurrent systemic therapy/radiation as a single agent for p16 (HPV)-positive for one of the following:
   a) T0-2, N1 (single node $\leq$3 cm) disease
   b) T0-2, N1 (single node >3 cm, or 2 or more ipsilateral nodes $\leq$6 cm), T0-2, N2 or T3,
   c) N0-2 disease
   d) T0-3, N3 or T4, N0-3; OR
6. Sequential systemic therapy/radiation as a single agent given weekly following induction chemotherapy for p16-negative for one of the following:
   a) T3-4a, N0-1 disease
   b) T1-4a, N2-3 disease; OR
7. Sequential systemic therapy/radiation as a single agent given weekly following induction chemotherapy for p16 (HPV)-positive for one of the following:
   a) T0-2, N1 (single node >3 cm, or 2 or more ipsilateral nodes $\leq$6 cm), T0-2, N2 or T3, N0-2 disease
   b) T0-3, N3 or T4, N0-3; OR
8. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin-ineligible for p16-negative for:
   a) T1-2, N0-1 disease with extranodal extension with or without positive margin or with positive margin alone
   b) T3-4a, N0-1 or T1-4a, N2-3 disease with extranodal extension and/or positive margin; OR
9. Postoperative systemic therapy combination with docetaxel if cisplatin-ineligible for p16 (HPV)-positive clinical disease for one of the following:
   a) T0-2, N0 or T0-2, N1 (single node $\leq$3 cm) disease with pathologic extranodal extension with or without positive margin or with positive margin alone
   b) T0-2, N1 (single node >3 cm, or 2 or more ipsilateral nodes $\leq$6 cm), T0-2, N2 or T3, N0-2 disease with pathologic extranodal extension and/or positive margin
   c) T0-3, N3 or T4, N0-3 disease with pathologic extranodal extension and/or positive margin

Cancer of the Supraglottic Larynx (Squamous Cell)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Primary concurrent systemic therapy/radiation as a single agent for one of the following:
   a) T3, N0 and most T3, N1-3 disease requiring (amenable to) total laryngectomy
   b) T1-2, N+ and selected T3, N1 disease amenable to larynx-preserving (conservation) surgery
   c) T4a, N0-3 disease for patients who decline surgery; OR
4. Sequential systemic therapy/radiation as a single agent given weekly following a partial response at the primary site to induction chemotherapy for one of the following:
   a) T3, N0 and most T3, N1-3 disease requiring (amenable to) total laryngectomy
   b) T1-2, N+ and selected T3, N1 disease amenable to larynx-preserving (conservation) surgery
   c) T4a, N0-3 disease for patients who decline surgery; OR
5. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin ineligible for most T1-2, N0, and selected T3 disease amenable to larynx-preserving (conservation) surgery for one of the following:
   a) Extranodal extension
   b) Discovery of a positive node for disease with a positive margin; OR
6. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin ineligible and extranodal extension and/or positive margin for one of the following:
   a) T3, N0 and most T3, N1-3 disease requiring (amenable to) total laryngectomy
   b) T1-2, N+ and selected T3, N1 disease amenable to larynx-preserving (conservation) surgery
   c) T4a, N0-3 disease
   d) T1-2, N+ and T3-4a, N0-3 disease following surgery with less than partial response at the primary to induction chemotherapy

Ethmoid Sinus Tumors

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Primary concurrent systemic therapy/radiation as a single agent for newly diagnosed T3-4a disease; OR
4. Primary concurrent systemic therapy/radiation as a single agent for one of the following:
   a) Newly diagnosed T3-4a disease
   b) Cancer diagnosed after incomplete resection and gross residual disease; OR
5. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin ineligible and positive margins for one of the following:
   a) Newly diagnosed T1-4a tumors after primary treatment with resection
   b) Newly diagnosed T3, T4a disease following less than a complete response (CR) to primary systemic therapy
   c) Cancer diagnosed after incomplete resection and gross residual disease
   d) Cancer diagnosed after incomplete resection and no residual disease on physical exam, imaging and/or endoscopy; OR

6. Sequential systemic therapy/radiation as a single agent given weekly following a complete response (CR) to primary systemic therapy for newly diagnosed T3, T4a disease

Maxillary Sinus Tumors

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin-ineligible for one of the following:
   a) T1-2, N0 tumors with all histologies except adenoid cystic and positive margins
   b) Positive margins or extranodal extension for T3-4a, N0 OR T1-4a, N+ disease

Occult Primary

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Initial definitive treatment as a single agent for N2-3 disease with poorly differentiated or non-keratinizing squamous cell, anaplastic (not thyroid), squamous cell carcinoma, or not otherwise specified (NOS) histology as one of the following:
   a) Concurrent systemic therapy/radiation
   b) Sequential systemic therapy/radiation given weekly following induction chemotherapy; OR
4. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin-ineligible for disease with extranodal extension after neck dissection of disease in levels IV or V with adenocarcinoma histology of neck node, thyroglobulin, and calcitonin negative; OR
5. Primary concurrent systemic therapy/radiation as a single agent for p16 (HPV)-positive for one of the following:
   a) N1 (single node $\leq$3 cm) disease
   b) N1 (single node >3 cm, or 2 or more ipsilateral nodes $\leq$6 cm) disease
   c) N2 disease
   d) N3 disease; OR
6. Sequential systemic therapy/radiation as a single agent given weekly following induction chemotherapy for p16 (HPV)-positive for one of the following:
   a) N1 (single node >3 cm, OR 2 or more ipsilateral nodes $\leq$6 cm) disease
   b) N2-3 disease; OR
7. Postoperative systemic therapy/radiation in combination with docetaxel if cisplatin ineligible for p16 (HPV)-positive clinical disease for one of the following:
   a) N0 disease with pathologic extranodal extension
   b) N1 (single node $\leq$3 cm) disease with pathologic extranodal extension
   c) N1 (single node >3 cm, or 2 or more ipsilateral nodes $\leq$6 cm) with pathologic extranodal extension
   d) N2-3 disease with extranodal extension

Very Advanced Head and Neck Cancer (Squamous Cell)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Primary concurrent systemic therapy/radiation for non-nasopharyngeal cancer as a single agent in patients with one of the following:
   a) Newly diagnosed T4b, N0-3, M0 disease with performance status (PS) 0-2
   b) Newly diagnosed unresectable nodal disease with no metastases and PS of 0-2
   c) Newly diagnosed non-metastatic disease for patients unfit for surgery and PS of 0-2
   d) Unresectable locoregional recurrence OR persistent disease without prior radiation therapy (RT) and PS of 0-2
   e) Limited metastases and metastatic (M1) disease at initial presentation with PS of 0-1
   f) Limited metastases and recurrent/persistent disease with distant metastases and a PS of 0-1
   g) Resectable locoregional recurrence or persistent disease without prior RT
   h) Unresectable locoregional recurrence, second primary, OR persistent disease with prior RT; OR
4. Sequential systemic therapy/radiation as a single agent given weekly following induction systemic therapy for non-nasopharyngeal cancer with performance status (PS) of 0-1 for one of the following:
   a) Newly diagnosed T4b, N0-3, M0 disease
   b) Newly diagnosed unresectable nodal disease with no metastases
   c) Newly diagnosed non-metastatic disease for patients who are unfit for surgery
   d) Unresectable locoregional recurrence or persistent disease in patients without prior radiation therapy (RT); OR
5. Sequential systemic therapy/radiation as a single agent given weekly following combination systemic therapy in patients with non-nasopharyngeal cancer for resectable locoregional recurrence or persistent disease without prior radiation therapy (RT); OR
6. Systemic therapy as a single agent for non-nasopharyngeal cancer as one of the following:
   a) First-line option for performance status (PS) 3 for newly diagnosed T4b, N0-3, M0 disease, newly diagnosed unresectable nodal recurrence with no metastases, newly diagnosed non-metastatic disease for patients unfit for surgery
   b) First-line or alternate subsequent-line option for metastatic (M1) disease at initial presentation and PS of 0-3
   c) First-line or subsequent-line option for unresectable locoregional recurrence without prior radiation therapy (RT), or unresectable persistent disease without prior RT and PS of 3
   d) First-line or alternate subsequent-line option for PS of 0-3 and unresectable locoregional recurrence with prior RT, unresectable second primary with prior RT, or unresectable persistent disease with prior RT, or recurrent/persistent disease with distant metastases; OR
7. Systemic therapy as first-line or subsequent-line option for non-nasopharyngeal cancer and a performance status (PS) of 0-1 for one of the following:
   a) Metastatic (M1) disease at initial presentation
   b) Recurrent/persistent disease with distant metastases
   c) Unresectable locoregional recurrence with prior radiation therapy (RT)
   d) Unresectable second primary with prior RT

e) Unresectable persistent disease with prior RT; AND
given in combination with one of the following:
i) Fluorouracil and cisplatin, or carboplatin
ii) Docetaxel and cisplatin, or carboplatin
iii) Paclitaxel and cisplatin, or carboplatin
iv) Cisplatin
v) Nivolumab
vi) Pembrolizumab; OR

8. Combination systemic therapy in non-nasopharyngeal cancer for resectable locoregional recurrence OR persistent disease without prior radiation therapy (RT) given with one of the following:
   a) Fluorouracil and cisplatin, or carboplatin
   b) Docetaxel and cisplatin, or carboplatin
   c) Paclitaxel and cisplatin, or carboplatin
   d) Cisplatin
   e) Nivolumab
   f) Pembrolizumab; OR
9. Systemic therapy as a first-line or subsequent-line (if not previously used) option for nasopharyngeal cancer and a performance status (PS) of 0-1, in combination with carboplatin for one of the following:
   a) Unresectable locoregional recurrence with prior radiation therapy (RT)
   b) Unresectable second primary with prior RT
   c) Unresectable persistent disease with prior RT
   d) Recurrent/persistent disease with distant metastases; OR
10. Postoperative systemic therapy/radiation in combination with docetaxel for non-nasopharyngeal cancer if cisplatin-ineligible and with extranodal extension and/or positive margin for one of the following:
    a) Resectable locoregional recurrence or persistent disease without prior radiation therapy (RT)
    b) Resectable locoregional recurrence, second primary, or persistent disease with prior radiation therapy [4]

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with afatinib as subsequent therapy for EGFR exon 19 deletion, or exon 21 L858R, or EGFR S768I, L861Q and/or G719X mutation positive recurrent, advanced, or metastatic disease who have one of the following:
   a) Have progressed on EGFR tyrosine kinase inhibitor therapy for asymptomatic disease, symptomatic brain lesions, or symptomatic systemic limited progression
   b) Are T790M negative, have progressed on EGFR tyrosine kinase inhibitor therapy, and have multiple symptomatic systemic lesions
   c) Are T790M positive, have progressed on osimertinib, and have multiple symptomatic systemic lesions [5]

Penile Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Single-agent as subsequent-line systemic therapy for metastatic disease [6]

Rectal Cancer (Adenocarcinoma)

1. At least 18 years of age; AND
2. Prescribed or in consultation with an oncologist; AND
3. Therapy for KRAS/NRAS/BRAF wild-type gene tumors in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CapeOx (capecitabine and oxaliplatin), or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if intensive therapy is recommended as adjuvant therapy for one of the following:
   a) After resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H)
   b) After resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy for dMMR/MSI-H only
   c) Unresectable metachronous metastases that converted to resectable disease after initial treatment for pMMR/MMS only, or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H; OR
4. Adjuvant treatment in combination with irinotecan for unresectable metachronous metastases (KRAS/NRAS/BRAF wild-type gene only) for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only that converted to resectable disease after initial treatment; OR
5. Adjuvant treatment in combination with encorafenib for unresectable metachronous metastases (BRAF V600E mutation positive) for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only that converted to resectable disease after initial treatment; OR
6. Therapy for KRAS/NRAS/BRAF wild-type gene tumors as a single agent if intensive therapy is not recommended as adjuvant treatment for one of the following:
   a) Following resection and/or local therapy for resectable metachronous metastases in patients who have received previous chemotherapy for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or ineligible for, or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H)
   b) Following resection and/or local therapy for resectable metachronous metastases in patients who have received previous immunotherapy for dMMR/MSI-H only
   c) Unresectable metachronous metastases that converted to resectable disease after initial treatment for pMMR/MMS only, or ineligible for or progression on checkpoint inhibitor immunotherapy for dMMR/MSI-H; OR

Note: Biologic therapy is only appropriate for continuation of a favorable response from conversion therapy.

7. Therapy for KRAS/NRAS/BRAF wild-type gene tumors in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CapeOx (capecitabine and oxaliplatin), or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for or progression on checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) if intensive therapy is recommended for one of the following:
    a) Primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with existing or imminent obstruction
    b) Primary treatment for synchronous unresectable metastases of other sites
    c) Primary treatment for unresectable isolated pelvic/anastomotic recurrence
    d) Initial treatment for unresectable metachronous metastases in patients who have not received previous therapy with FOLFOX or CapeOX within the past 12 months but received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, OR did not receive any previous chemotherapy
    e) Progression on non-intensive therapy, unless prior fluoropyrimidine received, with improvement in functional status; OR
8. Primary treatment for T3, Any N; T1-2, N1-2; T4, Any N; or locally unresectable or medically inoperable disease (KRAS/NRAS/BRAF wild-type gene only) if resection is contraindicated following total neoadjuvant therapy for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or ineligible for, or progression on a checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) or neoadjuvant/definitive immunotherapy for (dMMR/MSI-H) only if intensive therapy is recommended for one of the following:
    a) CapeOx (capecitabine and oxaliplatin) regimen
    b) FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen
    c) FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen; OR
9. Primary treatment for synchronous liver only and/or lung only metastases (KRAS/NRAS/BRAF wild-type gene only) for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) only and is not a candidate for immunotherapy that is unresectable or medically inoperable in combination with one of the following:
    a) FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
    b) FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen; OR
10. Initial treatment for unresectable metachronous metastases (KRAS/NRAS/BRAF wild-type gene only) for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months in combination with one of the following:
    a) Irinotecan
    b) FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen; OR
11. Initial treatment in combination with encorafenib for patients with unresectable metachronous metastases (BRAF V600E mutation-positive) for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only and previous FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; OR
12. Therapy for KRAS/NRAS/BRAF wild-type gene tumors as a single agent if intensive therapy is not recommended for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or

ineligible for or, progression on a checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability-high (dMMR/MSI-H) as one of the following:
   a) Primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with existing or imminent obstruction
   b) Primary treatment for synchronous unresectable metastases of other sites
   c) Primary treatment for unresectable isolated pelvic/anastomotic recurrence
   d) Initial treatment for unresectable metachronous metastases in patients who have not received previous therapy with FOLFOX or CapeOX within the past 12 months but received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or did not receive any previous chemotherapy; OR

13. Primary treatment as a single agent for T3, Any N; T1-2, N1-2; T4, Any N; or locally unresectable or medically inoperable disease (KRAS/NRAS/BRAF wild-type gene only) if resection is contraindicated following total neoadjuvant therapy for proficient mismatch repair/microsatellite-stable (pMMR/MMS) only, or ineligible for, or progression on a checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) or neoadjuvant/definitive immunotherapy for (dMMR/MSI-H) only if intensive therapy is not recommended; OR
14. Subsequent therapy for progression of advanced or metastatic disease (KRAS/NRAS/BRAF wild-type gene only) that is proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for or progression on a checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) in combination with one of the following:
   a) Irinotecan, FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen, or as a single agent for patients who cannot tolerate irinotecan, if previously treated with oxaliplatin-based therapy without irinotecan
   b) Irinotecan, FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CapeOX (capecitabine and oxaliplatin), or as a single agent for patients who cannot tolerate irinotecan, if previously treated with irinotecan-based therapy without oxaliplatin
   c) Irinotecan or as a single agent for patients who cannot tolerate irinotecan if previously treated with oxaliplatin and irinotecan
   d) Irinotecan or as a single agent for patients who cannot tolerate irinotecan if previously treated without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab; OR
15. Subsequent therapy in combination with encorafenib for progression of advanced or metastatic disease (BRAF V600E mutation-positive) for proficient mismatch repair/microsatellite-stable (pMMR/MMS), or ineligible for, or progression on a checkpoint inhibitor immunotherapy for deficient mismatch repair/micro-satellite instability high (dMMR/MSI-H) in patients previously treated with one of the following:
   a) Oxaliplatin-based therapy without irinotecan
   b) Irinotecan-based therapy without oxaliplatin
   c) With irinotecan and oxaliplatin
   d) Without irinotecan or oxaliplatin
   e) Without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab [7]

Squamous Cell Skin Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Given with concurrent radiation therapy as a single agent for one of the following:
   a) Locally advanced disease if residual disease present and further surgery not feasible
   b) Resected high-risk regional disease of the head and neck (pathologic extracapsular extension (ECE) or incompletely excised nodal disease)
   c) Regional disease that is unresectable, inoperable, or incompletely resected
   d) Regional recurrence or distant metastatic disease; OR
4. Single-agent therapy if ineligible for or progressed on immune checkpoint inhibitors and clinical trials as a treatment for one of the following:
   a) Complicated cases of locally advanced disease in which curative surgery and curative radiation therapy (RT) is not feasible
   b) Regional disease that is unresectable, inoperable, or incompletely resected if curative RT not feasible
   c) Regional recurrence or distant metastatic disease [8]

Note:

1. Coverage of cetuximab will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation, or when all criteria are met.
2. The patient should not have received prior treatment with cetuximab or panitumumab.

Authorization Period and Renewal Criteria

1. Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.
2. Initial Authorization Period: 12 months
3. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
4. Renewal Authorization Period: 12 months

Cetuximab: References

1. Cetuximab. https://www.ncbi.nlm.nih.gov/books/NBK459293. Accessed May 3, 2023.
2. Erbitux (Cetuximab) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf. Accessed May 3, 2023.
3. National Comprehensive Cancer Network Guidelines. Colon Cancer (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 3, 2023.
4. National Comprehensive Cancer Network Guidelines. Head and Neck Cancer (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed May 3,

2023.
5. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed May 3, 2023.
6. National Comprehensive Cancer Network. Penile Cancer. (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/penile.pdf. Accessed May 3, 2023.
7. National Comprehensive Cancer Network. Rectal Cancer. (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed May 3, 2023.
8. National Comprehensive Cancer Network. Squamous Cell Skin Cancer (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed May 3, 2023.

Cetuximab: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment.

CODE	DESCRIPTION
C10.9	Malignant neoplasm of oropharynx
C11.9	Malignant neoplasm of nasopharynx, unspecified
C14.8	Malignant neoplasm of overlapping sites of lip, oral cavity, and pharynx
C18.0	Malignant neoplasm of the colon
C20	Malignant neoplasm of the rectum
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C32.0	Malignant neoplasm of glottis
C32.1	Malignant neoplasm of supraglottis
C34.90	Malignant neoplasm of unspecified bronchus or lung
C44.92	Squamous cell carcinoma of skin, unspecified

C60.9	Malignant neoplasm of penis
C76.0	Malignant neoplasm of head, face, and neck
C80.1	Malignant (primary) neoplasm, unspecified
J9055	Cetuximab (Erbitux)

Cetuximab: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2023
2	Policy Review Dates:	5/3/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	9/13/2023
6	Revision Changes:	