Erbitux® (cetuximab)
(Intravenous)

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I. Length of Authorization [1,30]

Coverage will be provided for 6 months and may be renewed (unless otherwise specified).

Head and Neck Cancer

- In combination with radiation therapy: Coverage will be provided for the duration of radiation therapy (6-7 weeks).

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Erbitux 100 mg/50 mL solution for injection single-dose vial: 1 vial every 7 days
- Erbitux 200 mg/100 mL solution for injection single-dose vial: 5 vials x 1 dose, then 3 vials every 7 days

B. Max Units (per dose and over time) [HCPCS Unit]:

CRC, Head & Neck Cancer, & Squamous Cell Skin Cancer
– Load: 100 billable units x 1 dose – Maintenance Dose: 60 billable units every 7 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; AND

Colorectal Cancer (CRC) † ‡ [1,2,12,13,17,19,2e,5e-8e,10e-12e,15e]

- Patient is both KRAS and NRAS mutation negative (wild-type) as determined by FDA-approved or CLIA-compliant test❖; AND
- Will not be used as part of an adjuvant treatment regimen; AND

- Patient has not been previously treated with cetuximab or panitumumab; **AND**
- Will not be used in combination with an anti-VEGF agent (e.g., bevacizumab, ramucirumab); **AND**
  - Patient has metastatic, unresectable (or medically inoperable), or advanced disease that is BRAF mutation negative (wild-type); **AND**
    - Used as first-line therapy §; **AND**
      - Used in combination with FOLFIRI †; **OR**
      - Used in combination with CapeOx or FOLFOX; **AND**
        - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
        - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **OR**
      - Used in combination with an irinotecan-based regimen after previous FOLFOX or CapeOX within the past 12 months; **AND**
        - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
        - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for immunotherapy *(Note: Only applies to Colon Cancer)*; **OR**
    - Used as subsequent therapy; **AND**
      - Used in combination with irinotecan for irinotecan-refractory disease †; **OR**
      - Used as a single agent for oxaliplatin- and irinotecan-refractory disease †; **OR**
      - Used as a single agent for irinotecan-intolerant disease †; **OR**
      - Used in combination with irinotecan for oxaliplatin-refractory disease or oxaliplatin- and irinotecan-refractory disease §; **AND**
        - Patient has one of the following:
          - Mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
          - Mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **AND**

<u>In combination with irinotecan for oxaliplatin-refractory disease ONLY:</u>

- Patient must demonstrate an inadequate response to bevacizumab (*or a commercially available bevacizumab biosimilar agent*) in combination with irinotecan, unless there is a contraindication or intolerance, prior to approval of cetuximab; **OR**

- Used in combination with FOLFIRI for oxaliplatin-refractory disease §**; **AND**
  - Patient has one of the following:
    - Mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
    - Mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **AND**

> - Use of cetuximab will be restricted to patients with a contraindication or intolerance to bevacizumab (*or a commercially available bevacizumab biosimilar agent*) in combination with either FOLFIRI or FOLFOX; **OR**

- Used in combination with FOLFOX or CapeOx for irinotecan-refractory disease §**; **AND**
  - Patient has one of the following:
    - Mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
    - Mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for or has progressed on checkpoint inhibitor immunotherapy; **AND**

> - Use of cetuximab will be restricted to patients with a contraindication or intolerance to bevacizumab (*or a commercially available bevacizumab biosimilar agent*) in combination with either FOLFIRI or FOLFOX; **OR**

- Patient has BRAF V600E mutation positive disease as determined by an FDA-approved or CLIA-compliant test❖ †; **AND**
  - Used in combination with encorafenib; **AND**
    - Used as subsequent therapy for progression of advanced or metastatic disease after at least one prior line of treatment in the advanced or metastatic disease setting; **OR**
    - Used as initial treatment for unresectable metastatic disease after previous adjuvant FOLFOX or CapeOX within the past 12 months; **AND**
      - Patient has mismatch repair proficient/microsatellite-stable (pMMR/MSS) disease; **OR**
      - Patient has mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) disease AND is not a candidate for immunotherapy *(Note: Only applies to Colon Cancer)*

***May also be used for progression on non-intensive therapy, except if received previous fluoropyrimidine, with improvement in functional status (Note: Step therapy does not apply if patient had progression on non-intensive therapy).*

§ *Colon cancer patients must have left-sided tumors only.*

Head and Neck Cancer † ‡ Φ [1,2,14,16,25,29,30,17e-23e,25e-29e]

- Patient has squamous cell carcinoma; **AND**
  - Used in combination with radiation as a single agent †; **AND**

    ▪ Use of cetuximab in combination with radiation therapy for first-line treatment will be restricted to patients with a contraindication or intolerance to cisplatin- or carboplatin-based therapy; **OR**
  - Used as first-line therapy; **AND**
    - Used in combination with platinum-based therapy †; **AND**

      – Use of cetuximab will be restricted to patients with a contraindication or intolerance to one of the following regimens:
        - Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU
        - Pembrolizumab monotherapy *(patients with CPS ≥1 only)*
        - Generically available agent/regimen (e.g., cisplatin/paclitaxel, etc. *[see NCCN Head and Neck Cancers guideline for complete list of alternatives]*); **OR**
    - Used in combination with nivolumab for very advanced head and neck cancer* (non-nasopharyngeal) and PS 0-1; **AND**

      – Use of cetuximab will be restricted to patients with a contraindication or intolerance to one of the following:
        - Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU
        - Pembrolizumab monotherapy *(patients with CPS ≥1 only)*
        - Generically available agent/regimen (e.g., cisplatin/paclitaxel, etc. *[see NCCN Head and Neck Cancers guideline for complete list of alternatives]*); **OR**
  - Used as subsequent therapy; **AND**
    - Used as a single agent after failure on platinum-based therapy †; **AND**

      ▪ Use of cetuximab after failure on platinum-based therapy will be restricted to patients with a contraindication or intolerance to one of the following, if not previously used:
        – Pembrolizumab *(patients with CPS ≥1 only)*
        – Nivolumab *(patients with PD-L1 ≥1 only)*

** Very Advanced Head and Neck Cancers include: newly diagnosed locally advanced T4b [M0] disease; newly diagnosed unresectable regional nodal disease, typically N3; metastatic disease at initial presentation [M1]; or recurrent or persistent disease.*

Squamous Cell Skin Cancer ‡ [2,21,27]

- Used as a single agent without radiation therapy; **AND**
- Patient is ineligible for or progressed on immune checkpoint inhibitor therapy and clinical trials; **AND**
- Patient is chemotherapy-naive; **AND**
  - Patient has locally advanced disease and curative surgery and curative radiation therapy are not feasible; **OR**
  - Patient has unresectable disease AND curative radiation therapy is not feasible; **OR**
  - Patient has regional recurrence or distant metastatic disease

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

❖ *If confirmed using an FDA approved assay – http://www.fda.gov/companiondiagnostics*

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,30]

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion reactions/anaphylactic reactions, cardiopulmonary arrest, pulmonary toxicity/interstitial lung disease, dermatologic toxicity, hypomagnesemia/electrolyte abnormalities, etc.

Head and Neck Cancer (in combination with radiation therapy)

- Patient has not exceeded a maximum of 7 weeks of therapy

V. Dosage/Administration [1,12,13,20-23,29,30]

Indication	Dose

Colorectal Cancer	400 mg/m² loading dose intravenously, then 250 mg/m² intravenously every 7 days until disease progression or unacceptable toxicity **OR** 500 mg/m² intravenously every 14 days until disease progression or unacceptable toxicity
Head and Neck Cancer	In combination with radiation therapy: 400 mg/m² loading dose intravenously, then 250 mg/m² intravenously every 7 days for the duration of radiation therapy (6-7 weeks) Monotherapy or in combination with platinum-based therapy: 400 mg/m² loading dose intravenously, then 250 mg/m² intravenously every 7 days until disease progression or unacceptable toxicity **OR** 500 mg/m² intravenously every 14 days until disease progression or unacceptable toxicity In combination with nivolumab: 500 mg/m² intravenously every 14 days until disease progression or unacceptable toxicity
Squamous Cell Skin Cancer	400 mg/m² loading dose intravenously, then 250 mg/m² intravenously every 7 days until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9055 – Injection, cetuximab, 10 mg; 1 billable unit = 10 mg

NDC(s):

- Erbitux 100 mg/50 mL single-dose vial; solution for injection: 66733-0948-xx
- Erbitux 200 mg/100 mL single-dose vial; solution for injection: 66733-0958-xx

VII. References (STANDARD)

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2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) cetuximab. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed June 2023.
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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C00.0	Malignant neoplasm of external upper lip
C00.1	Malignant neoplasm of external lower lip
C00.2	Malignant neoplasm of external lip, unspecified

ICD-10	ICD-10 Description
C00.3	Malignant neoplasm of upper lip, inner aspect
C00.4	Malignant neoplasm of lower lip, inner aspect
C00.5	Malignant neoplasm of lip, unspecified, inner aspect
C00.6	Malignant neoplasm of commissure of lip, unspecified
C00.8	Malignant neoplasm of overlapping sites of lip
C00.9	Malignant neoplasm of lip, unspecified
C01	Malignant neoplasm of base of tongue
C02.0	Malignant neoplasm of dorsal surface of tongue
C02.1	Malignant neoplasm of border of tongue
C02.2	Malignant neoplasm of ventral surface of tongue
C02.3	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
C02.4	Malignant neoplasm of lingual tonsil
C02.8	Malignant neoplasm of overlapping sites of tongue
C02.9	Malignant neoplasm of tongue, unspecified
C03.0	Malignant neoplasm of upper gum
C03.1	Malignant neoplasm of lower gum
C03.9	Malignant neoplasm of gum, unspecified
C04.0	Malignant neoplasm of anterior floor of mouth
C04.1	Malignant neoplasm of lateral floor of mouth
C04.8	Malignant neoplasm of overlapping sites of floor of mouth
C04.9	Malignant neoplasm of floor of mouth, unspecified
C05.0	Malignant neoplasm of hard palate
C05.1	Malignant neoplasm of soft palate
C05.8	Malignant neoplasm of overlapping sites of palate
C05.9	Malignant neoplasm of palate, unspecified
C06.0	Malignant neoplasm of cheek mucosa
C06.2	Malignant neoplasm of retromolar area
C06.80	Malignant neoplasm of overlapping sites of unspecified parts of mouth
C06.89	Malignant neoplasm of overlapping sites of other parts of mouth
C06.9	Malignant neoplasm of mouth, unspecified
C09.0	Malignant neoplasm of tonsillar fossa
C09.1	Malignant neoplasm of tonsillar pillar (anterior) (posterior)
C09.8	Malignant neoplasm of overlapping sites of tonsil
C09.9	Malignant neoplasm of tonsil, unspecified
C10.0	Malignant neoplasm of vallecula
C10.1	Malignant neoplasm of anterior surface of epiglottis
C10.2	Malignant neoplasm of lateral wall of oropharynx
C10.3	Malignant neoplasm of posterior wall of oropharynx

ICD-10	ICD-10 Description
C10.4	Malignant neoplasm of branchial cleft
C10.8	Malignant neoplasm of overlapping sites of oropharynx
C10.9	Malignant neoplasm of oropharynx, unspecified
C11.0	Malignant neoplasm of superior wall of nasopharynx
C11.1	Malignant neoplasm of posterior wall of nasopharynx
C11.2	Malignant neoplasm of lateral wall of nasopharynx
C11.3	Malignant neoplasm of anterior wall of nasopharynx
C11.8	Malignant neoplasm of overlapping sites of nasopharynx
C11.9	Malignant neoplasm of nasopharynx, unspecified
C12	Malignant neoplasm of pyriform sinus
C13.0	Malignant neoplasm of postcricoid region
C13.1	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
C13.2	Malignant neoplasm of posterior wall of hypopharynx
C13.8	Malignant neoplasm of overlapping sites of hypopharynx
C13.9	Malignant neoplasm of hypopharynx, unspecified
C14.0	Malignant neoplasm of pharynx, unspecified
C14.2	Malignant neoplasm of Waldeyer's ring
C14.8	Malignant neoplasm of overlapping sites of lip, oral cavity and pharynx
C18.0	Malignant neoplasm of cecum
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C30.0	Malignant neoplasm of nasal cavity
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
C32.2	Malignant neoplasm of subglottis
C32.3	Malignant neoplasm of laryngeal cartilage
C32.8	Malignant neoplasm of overlapping sites of larynx

ICD-10	ICD-10 Description
C32.9	Malignant neoplasm of larynx, unspecified
C44.00	Unspecified malignant neoplasm of skin of lip
C44.02	Squamous cell carcinoma of skin of lip
C44.09	Other specified malignant neoplasm of skin of lip
C44.121	Squamous cell carcinoma of skin of unspecified eyelid, including canthus
C44.1221	Squamous cell carcinoma of skin of right upper eyelid, including canthus
C44.1222	Squamous cell carcinoma of skin of right lower eyelid, including canthus
C44.1291	Squamous cell carcinoma of skin of left upper eyelid, including canthus
C44.1292	Squamous cell carcinoma of skin of left lower eyelid, including canthus
C44.221	Squamous cell carcinoma of skin of unspecified ear and external auricular canal
C44.222	Squamous cell carcinoma of skin of right ear and external auricular canal
C44.229	Squamous cell carcinoma of skin of left ear and external auricular canal
C44.320	Squamous cell carcinoma of skin of unspecified parts of face
C44.321	Squamous cell carcinoma of skin of nose
C44.329	Squamous cell carcinoma of skin of other parts of face
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.520	Squamous cell carcinoma of anal skin
C44.521	Squamous cell carcinoma of skin of breast
C44.529	Squamous cell carcinoma of skin of other part of trunk
C44.621	Squamous cell carcinoma of skin of unspecified upper limb, including shoulder
C44.622	Squamous cell carcinoma of skin of right upper limb, including shoulder
C44.629	Squamous cell carcinoma of skin of left upper limb, including shoulder
C44.721	Squamous cell carcinoma of skin of unspecified lower limb, including hip
C44.722	Squamous cell carcinoma of skin of right lower limb, including hip
C44.729	Squamous cell carcinoma of skin of left lower limb, including hip
C44.82	Squamous cell carcinoma of overlapping sites of skin
C44.92	Squamous cell carcinoma of skin, unspecified
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D37.01	Neoplasm of uncertain behavior of lip
D37.02	Neoplasm of uncertain behavior of tongue
D37.05	Neoplasm of uncertain behavior of pharynx
D37.09	Neoplasm of uncertain behavior of other specified sites of the oral cavity

ICD-10	ICD-10 Description
D38.0	Neoplasm of uncertain behavior of larynx
D38.5	Neoplasm of uncertain behavior of other respiratory organs
D38.6	Neoplasm of uncertain behavior of respiratory organ, unspecified
Z85.038	Personal history of other malignant neoplasm of large intestine

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC