naxitamab (Danyelza®)

Policy # 00747
Original Effective Date: 06/14/2021
Current Effective Date: 06/10/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of naxitamab (Danyelza®)‡ for the treatment of high-risk neuroblastoma to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for naxitamab (Danyelza) will be considered when the following criteria are met:

- Patient has a diagnosis of high-risk neuroblastoma in the bone or bone marrow; AND
- Disease is relapsed or refractory to prior therapy; AND
- Patient has previously responded to therapy (i.e., partial response, minor response, or stable disease); AND
- Patient is 1 year of age or older; AND
- Drug will be used in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF); AND
- Dose will not exceed 450 mg per treatment cycle (e.g., 150 mg/day on Days 1, 3, and 5 of each cycle).

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers naxitamab (Danyelza) when the patient selection criteria are not met to be **investigational.***

Background/Overview

Danyelza is a glycolipid disialoganglioside (GD2) binding monoclonal antibody that is indicated in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) for relapsed or refractory high-risk neuroblastoma in the bone or bone marrow following a partial response (PR), minor response (MR), or stable disease (SD) in patients ≥1 year of age. It is the second GD2 monoclonal antibody approved for this condition with the first being Unituxin. The recommended dose of Danyelza is 3 mg/kg/day (up to 150 mg/day) administered by intravenous infusion on Days 1, 3, and 5 of each treatment cycle in combination with GM-CSF. GM-CSF should be administered as 250 µg/m^2/day starting 5 days before Danyelza injection and then 500 µg/m^2/day should be given on Days 1-5 of each cycle. Cycles are repeated once every 4 weeks until complete response (CR) or PR, followed by five additional cycles once every 4 weeks. Subsequent cycles can be repeated every 8 weeks until disease progression or unacceptable adverse events.

Neuroblastoma is a cancer that originates from primordial neural crest cells that develop into sympathetic neural ganglia and adrenal medulla. It is a rare cancer, with about 700 cases diagnosed in the US each year. Approximately 90% of cases are diagnosed in children <5 years of age. Signs and symptoms of neuroblastoma vary depending on the tumor location. About one-half of patients are diagnosed with high-risk neuroblastoma which has a 5-year survival rate of 40% to 50%. The treatment of neuroblastoma is divided into three phases. In the induction phase, treatment includes chemotherapy with anthracyclines, alkylating agents, platinum compounds, and topoisomerase II inhibitors, along with surgical resection. In the consolidation phase, treatment includes myeloablative chemotherapy and autologous stem cell transplantation. During the post-consolidation phase, patients are treated with a variety of agents, including Unituxin (a GD2-binding monoclonal antibody), to reduce the risk of tumor recurrence. While Unituxin and Danyelza have similar mechanisms of action, they cannot be compared directly because they have not been compared in clinical trials. Additionally, their indications differ slightly with Unituxin only indicated

in combination with GM-CSF, interleukin-2, and 13-cis-retinoic acid. Additionally, Unituxin is dosed differently than Danyelza and requires a 10-20 hour infusion to be given daily on the first four days of each cycle. In comparison, Danyelza only requires a 30-minute infusion on Days 1, 3, and 5 of each cycle.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Danyelza was approved in November 2020 for use in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Danyelza in combination with GM-CSF was evaluated in two open-label, single arm trials in patients with high-risk neuroblastoma with refractory or relapsed disease in the bone or bone marrow, Study 201 and Study 12-230.

Study 201 was a multicenter trial in a subpopulation of patients who had refractory or relapsed high-risk neuroblastoma and demonstrated a partial response, minor response, or stable disease to prior therapy. Patients with progressive disease were excluded. All patients received at least one systemic therapy to treat disease outside of the bone or bone marrow prior to enrollment. Patients received Danyelza 9 mg/kg/cycle administered as three separate intravenous infusions of 3 mg/kg on Days 1, 3, and 5 of each cycle. Patients received GM-CSF subcutaneously at 250 µg/m^2/day on Days -4 to 0 and 500 µg/m^2/day on Days 1 to 5. Preplanned radiation to the primary site was allowed.

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The major efficacy outcome measure was overall response rate according to the revised International Neuroblastoma Response Criteria (INRC), as determined by independent pathology and imaging review and confirmed by at least one subsequent assessment. An additional efficacy outcome measure was duration of response (DOR). Of the 22 patients included in the efficacy analysis, 64% had refractory disease and 36% had relapsed disease. The median age was 5 years (range 3 to 10 years). The overall response rate in these patients was 45% and the median duration of response was 6.2 months.

Study 12-230 was a single center trial in a subpopulation of patients who had relapsed or refractory high-risk neuroblastoma in bone or bone marrow and demonstrated a partial response, minor response, or stable disease to prior therapy. Patients with progressive disease were excluded. All patients received at least one systemic therapy to treat disease outside of the bone or bone marrow prior to enrollment. Patients received Danyelza 9 mg/kg/cycle administered as 3 separate infusions of 3 mg/kg (on Days 1, 3, and 5) in the first week of each cycle. Patients received GM-CSF subcutaneously at 250 µg/m^2/day on Days -4 to 0 and 500 µg/m^2/day on Days 1 to 5. Radiation to non-target bony lesions and soft tissue lesions was permitted at the investigator's discretion; assessment of response excluded sites that received radiation.

The major efficacy outcome measures were overall response rate and duration of response (DOR) as determined by independent pathology and imaging review according to the revised INRC and confirmed by at least one subsequent assessment. Of the 38 patients included in the efficacy analysis, 55% had relapsed neuroblastoma and 45% had refractory disease. The median age was 5 years (range 2 to 23 years). The overall response rate in these patients was 34% and 23% of them experienced a duration of response ≥6 months.

References

1. Danyelza [package insert]. Y-mAbs Therapeutics, Inc. New York, NY. Updated January 2021.
2. Danyelza Drug Evaluation. Express Scripts. Updated January 2021.

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Policy History

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05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. New policy.
06/21/2021	Coding update
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy

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Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J9348 Delete codes effective 06/01/2023: C9399, J3490, J3590, J9999
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.