09-J3000-92

Original Effective Date: 03/15/21

Reviewed: 03/09/22

Revised: 04/15/22

Subject: Naxitamab-gqgk (Danyelza) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Neuroblastoma is the most common extracranial solid tumor in childhood with 90% of cases diagnosed at younger than 5 years of age. The yearly incidence is approximately 10.54 cases per 1 million in children younger than 15 years and prevalence about 1 case per 7,000 live births. The neuroblastoma originates in the adrenal medulla or the paraspinal sites where sympathetic nervous system tissue resides. Patients commonly present with an abdominal mass and up to 70% have metastatic disease at diagnosis. Prognosis depends on patient age, site of the primary tumor, tumor histology, regional lymph node involvement, stage of disease, response to treatment, and biological features.

Naxitamab-gqgk (Danyelza) is FDA-approved in combination with granulocyte-macrophage colony-stimulating factor (GMCSF), 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. The FDA-indication is contingent upon clinical benefit in confirmatory trials. Naxitamab-gqgk is a recombinant humanized monoclonal antibody that binds to the glycolipid disialoganglioside (GD2). This glycolipid is overexpressed on neuroblastoma cells and on normal cells of neuroectodermal origin, including the central nervous system and peripheral nerves. GD2 binding induces cell lysis of GD2-expressing cells through antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

The efficacy of naxitamab-gqgk was evaluated in patients with relapsed or refractory neuroblastoma in the bone or bone marrow in two single-arm, open-label trials (study 1 and study 2). Patients with progressive disease following their most recent therapy were excluded. All patients had received at least one systemic therapy to treat disease outside of the bone or bone marrow prior to trial enrollment. Patients were permitted to receive pre-planned radiation to the primary disease site in study 1 and radiation therapy to non-target bony lesions or soft tissue disease in study 2. Among 22 patients in study

1, there were 64% with refractory disease, 36% with relapsed disease and the median age was 5 years (range 3 to 10 years). In study 2, there were 38 patients of which 55% had relapsed neuroblastoma, 45% with refractory disease, and the median age was 5 years (range 2 to 23 years). Both trials included patients with prior treatments such as surgery, chemotherapy, radiation, autologous stem cell transplant, or prior anti-GD2 antibody treatment. The main efficacy outcome measures were confirmed overall response rate (ORR) per the revised International Neuroblastoma Response Criteria (INRC) and duration of response (DOR). In study 1, the ORR was 45% (95% CI: 24%, 68%) and 30% of responders had a DOR greater or equal to 6 months. In study 2, the ORR was 34% (95% CI: 20%, 51%) with 23% of patients having a DOR greater or equal to 6 months. For both trials, responses were observed in either the bone, bone marrow or both.

Serious adverse reactions occurred in both studies and the most frequently occurring in study 1 included anaphylactic reaction (12%) and pain (8%) and in study 2 were hypertension (14%), hypotension (11%), and pyrexia (8%) Naxitamab-gqgk contains a black box warning for serious infusion-related reactions including cardiac arrest, anaphylaxis, hypotension, bronchospasm and stridor. It also contains a black box warning for severe neurotoxicity, transverse myelitis and reversible leukoencephalopathy syndrome (RPLS). Premedications are required to prevent infusion reactions, neuropathic pain, and nausea/vomiting.

POSITION STATEMENT:

Initiation of naxitamab-gqgk (Danyelza) injection **meets the definition of medical necessity** with **ANY** of the following conditions when **ALL** associated criteria are met:

1. Relapsed or refractory high-risk neuroblastoma in the bone or bone marrow
    a. Member is diagnosed with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow
    b. Member demonstrated a partial response, minor response, or stable disease to one prior systemic therapy
    c. Naxitamab-gqgk is use is in combination with a granulocyte-macrophage colony-stimulating factor (i.e., sargramostim)
    d. Naxitamab-gqgk is used in combination with premedications to mitigate the risk of infusion reactions (e.g., corticosteroids) and neurotoxicity (e.g., gabapentin)
    e. Naxitamab-gqgk is not used in combination with dinutuximab (Unituxin)
    f. The dose does not exceed 3 mg/kg/day on Day 1, 3, and 5 every 4 weeks of each treatment cycle until complete or partial response. Five additional treatment cycles are given every 4 weeks following a complete or partial response and then subsequent cycles every 8 weeks
2. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    a. Member meets one of the following:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND

member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. The dose does not exceed 3 mg/kg/day on Day 1, 3, and 5 every 4 weeks of each treatment cycle until complete or partial response. Five additional treatment cycles are given every 4 weeks following a complete or partial response and then subsequent cycles every 8 weeks

Approval duration: 6 months

Continuation of naxitamab-gqgk (Danyelza) injection **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. An authorization or reauthorization for naxitamab-gqgk (Danyelza) injection has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of relapsed or refractory high-risk neuroblastoma in the bone or bone marrow or other FDA-approved or NCCN supported diagnosis; **OR** the member has previously met **ALL** indication-specific criteria.
2. The member has a beneficial response to treatment (i.e., no disease progression or toxicity)
3. Naxitamab-gqgk is not used in combination with dinutuximab (Unituxin)
4. The dose does not exceed 3 mg/kg/day on Day 1, 3, and 5 every 4 weeks of each treatment cycle until complete or partial response. Five additional treatment cycles are given every 4 weeks following a complete or partial response and then subsequent cycles every 8 weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Naxitamab-gqgk is FDA-approved in combination with granulocyte-macrophage colony-stimulating factor (GMCSF), 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.
- The recommended dosage is 3 mg/kg/day (up to 150 mg/day), administered as an intravenous infusion after dilution on Days 1, 3, and 5 of each treatment cycle. Treatment cycles are repeated every 4 weeks until complete response or partial response, followed by 5 additional cycles every 4 weeks. Subsequent cycles may be repeated every 8 weeks.
- Pain Management Prior to and During Infusion:
    - Five days prior to the first infusion in each cycle, initiate a 12-day course (Day -4 through Day 7) of prophylactic medication for neuropathic pain, such as gabapentin.

    - Administer oral opioids 45-60 minutes prior to initiation of the infusion and additional intravenous opioids as needed for breakthrough pain during the infusion.
    - Consider use of ketamine for pain that is not adequately controlled by opioids.
- Premedication: Reduce Risk of Infusion-Related Reactions and Nausea/Vomiting
    - Administer intravenous corticosteroids (e.g. methylprednisolone 2 mg/kg with maximum dose of 80 mg or equivalent corticosteroid dose) 30 minutes to 2 hours prior to the first infusion
    - Administer corticosteroid premedication for subsequent infusions if a severe infusion reaction occurredwith the previous infusion or during the previous cycle.
    - Administer an antihistamine, an H2 antagonist, acetaminophen and an antiemetic 30 minutes prior to each infusion.

Dose Adjustments

- See prescribing information for dose modifications in response to adverse events.

Drug Availability

- Injection: 40 mg/10 mL (4 mg/mL) in a single-dose vial.

PRECAUTIONS:

Boxed Warning

- Serious Infusion-Related Reactions: serious infusion reactions, including cardiac arrest, anaphylaxis, hypotension, bronchospasm, and stridor may occur. Premedicate prior to each infusion as recommended. Reduce the rate, interrupt infusion, or permanently discontinue based on severity.
- Neurotoxicity: severe neurotoxicity,including severe neuropathic pain, transverse myelitis, and reversible posterior leukoencephalopathy syndrome (RPLS) may occur.Premedicate to treat neuropathic pain as recommended. Permanently discontinue based on the adverse reaction and severity.

Contraindications

- History of severe hypersensitivity reaction to naxitamab-gqgk

Precautions/Warnings

- Neurotoxicity: Peripheral neuropathy, neurological disorders of the eye, and prolonged urinary retention have also occurred. Permanently discontinue as recommended
- Hypertension: Monitor blood pressure during and after infusion as recommended. Withhold, reduce infusion rate, or discontinue based on severity.
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception

BILLING/CODING INFORMATION:

HCPCS Coding

J9348	Injection, naxitamab-gqgk, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C74.90	Malignant neoplasm of unspecified part of the adrenal gland

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Complete Response: No evidence of disease, including resolution of MIBG uptake (or PET scan positivity in MIBG non-avid disease) in any location of soft tissue or bone, with less than 10 mm remaining on 3-D imaging of primary tumor; target lymph nodes less than 10 mm in short dimension; and no histologic tumor in two bone marrow biopsies and two bone marrow aspirates.

Minor Response: Partial response or complete response of at least one component of disease, but at least one other component with stable disease **and** no component with progressive disease.

Partial Response: 30% or more decrease in longest diameter of primary site **and** no new lesions **and** MIBG (or 18F-FDG PET) stable or improved **and** at least a 50% reduction in absolute MIBG bone score or a 50% or greater reduction in number of 18F-FDG PET-avid bone lesions.

Progressive Disease: Any new lesion; increase in longest diameter in any measurable lesion by 20% **and** increase of at least 5 mm in longest diameter; previous negative bone marrow now positive for tumor; any new soft tissue lesion that is MIBG (or 18F-FDG PET) avid or positive by biopsy; a new avid bone site; **or** increase in relative MIBG score of 1.25% or greater.

Stable Disease: Neither sufficient shrinkage for partial response nor sufficient increase for progressive disease and may have greater than 5% tumor infiltration as defined in minimal disease.

RELATED GUIDELINES:

Dinutuximab (Unituxin™), 09-J2000-42

OTHER:

None

REFERENCES:

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3. Kushner BH, Modak S, Ellen M. Basu EM,et al. High-dose naxitamab plus stepped-up dosing of GM-CSF for high-risk neuroblastoma (HR-NB): Efficacy against histologically-evident primary refractory metastases in bone marrow (BM). Journal of Clinical Oncology 2019 37:15_suppl, 10024-10024.
4. Micromedex® Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 02/23/22.
5. Mora J, Chan GCF, Morgenstern DA, et al. Naxitamab, a new generation anti-GD2 monoclonal antibody (mAb) for treatment of relapsed/refractory high-risk neuroblastoma (HR-NB). Journal of Clinical Oncology 2020 38:15_suppl, 10543-10543.
6. National Cancer Institute: Neuroblastoma. http://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq#section/_1 Accessed 01/27/21.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/09/22.

GUIDELINE UPDATE INFORMATION:

03/15/21	New Medical Coverage Guideline.
07/01/21	Revision: Added HCPCS code J9348 and deleted codes C9399 and J9999.
04/15/22	Review and revision to guideline; consisting of updating the references.