NEW DRUG APPROVAL

Brand Name	Danyelza®
Generic Name	naxitamab-gqgk
Drug Manufacturer	Y-mAbs Therapeutics, Inc.

New Drug Approval

FDA Approval Date: November 25, 2020

Review Designation: Orphan drug

Type of Review: Biologic License Application (BLA): 761171

Dispensing Restrictions: Speciality only, Limited distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Neuroblastoma is a cancer that develops from immature nerve cells found in several areas of the body. Neuroblastoma most commonly arises in and around the adrenal glands, which have similar origins to nerve cells and sit atop the kidneys. However, neuroblastoma can also develop in other areas of the abdomen and in the chest, neck and near the spine, where groups of nerve cells exist.

Neuroblastoma most commonly affects children age 5 or younger, though it may rarely occur in older children. Neuroblastoma is almost exclusively a disease of children. It is the third most common childhood cancer, after leukemia and brain tumors, and is the most common solid extracranial tumor in children. More than 600 cases are diagnosed in the United States each year, and neuroblastoma accounts for approximately 15% of all pediatric cancer fatalities.

Incidence rates are age dependent. The median age at diagnosis is 17.3 months, and 40% of patients are diagnosed before one year of age. Neuroblastomas are the most common extracranial solid malignant tumor diagnosed during the first two years of life, and the most common cancer among infants younger than 12 months, in whom the incidence rate is almost twice that of leukemia (58 versus 37 per one million infants). The incidence of neuroblastoma is greater among white than black infants (ratio of 1.7 and 1.9 to 1 for males and females, respectively), but little if any racial difference is apparent among older children [4]. Neuroblastoma is slightly more common among boys compared with girls.

Efficacy

Initial results from the Study 12-230 trial (NCT01757626) had been presented at the 2019 International Society of Pediatric Oncology Annual Congress. At the meeting, data from several subsets of patients who received the agent were released.

In 28 patients with primary refractory high-risk neuroblastoma, the overall response rate (ORR) as 78% and the 2-year PFS rate was 50%. In a subset of 35 patients with relapsed neuroblastoma resistant to salvage therapy, the ORR was 37% and the 2-year PFS rate was 36%. In 44 patients with high-risk neuroblastoma in second or later complete remission and no evidence of disease, naxitamab-gqgk was given in combination with GM-CSF as maintenance therapy; this resulted in a 2-year PFS rate of 52%.

Findings from a trial (NCT03363373) detailed in a poster presentation that had recently been presented at the 2020 ASCO Virtual Meeting showed that treatment with the agent in 24 patients with relapsed/refractory high-risk

neuroblastoma led to a high complete response (CR) rate of 71% (95% CI, 49%-87%) and an overall objective response rate (ORR) of 79 (95% CI, 58%-93%).

Of 16 patients who were primary refractory, the ORR with naxitamab-gqgk was 88% (95% CI, 62%-98%) and the CR rate was 81% (95% CI, 54%-96%). Of 8 patients who had an incomplete response to salvage treatment, the ORR and CR rates were 63% (95% CI, 24%-91%) and 50% (95% CI, 16%-84%), respectively. 13 of 14 patients who had bone marrow disease at baseline experienced bone marrow clearance.

The median progression-free survival (PFS) was 42 weeks (95% CI, 26–not estimable), and the median follow-up time in patients evaluable for efficacy was 30 weeks.

Study 201 and Study 12-230: Study Design Summary

	Study 201 (NCT03363373)	Study 12-230 (NCT01757626)
Interventions	• Danyelza 9 mg/kg/cycle administered as three separate IV infusions of 3 mg/kg on Days 1, 3, and 5 of each cycle • Patients received GM-CSF SC at 250 µg/m²/day on Days –4 to 0 and at 500 µg/m²/day on Days 1 to 5 • Preplanned radiation to the primary site was allowed	• Danyelza 9 mg/kg/cycle administered as three separate IV infusions of 3 mg/kg on Days 1, 3, and 5 in the first week of each cycle • Patients received GM-CSF SC at 250 µg/m²/day on Days –4 to 0 and at 500 µg/m²/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
Endpoints	• **Primary:** ORR according to the revised INRC, as determined by independent pathology and imaging review and confirmed by at least one subsequent assessment • **Secondary:** DOR	• **Primary:** Maximum tolerated dosage, ORR, and DOR according to the revised INRC, as determined by independent pathology and imaging review and confirmed by at least one subsequent assessment • **Secondary:** Pharmacokinetics of an antibody called humanized 3F8 (hu3F8)
Efficacy and Safety Results	• ORR was 45% (95% CI: 24%, 68%), and 30% of responders had a DOR ≥6 months • In an exploratory analysis in the subset of patients previously treated with an anti-GD2 antibody (n = 4), one patient demonstrated a confirmed CR, and no patients demonstrated a PR	• ORR was 34% (95% CI: 20%, 51%), with 23% of patients having a DOR ≥6 months • In an exploratory analysis in the subset of patients previously treated with an anti-GD2 antibody (n = 22), ORR was 18% (95% CI: 5%, 40%); no patients had a documented response of 6 months or greater

Safety

ADVERSE EVENTS

The most common adverse reactions (≥25%) are infusion-related reaction, pain, tachycardia, vomiting, cough, nausea, diarrhea, decreased appetite, hypertension, fatigue, erythema multiforme, peripheral neuropathy, urticaria, pyrexia, headache, injection site reaction, edema, anxiety, localized edema, and irritability.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) are decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased platelet count, decreased potassium, increased alanine aminotransferase, decreased glucose, decreased calcium, decreased albumin, decreased sodium, and decreased phosphate.

WARNINGS & PRECAUTIONS

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.

CONTRAINDICATIONS

History of severe hypersensitivity reaction to naxitamab-gqgk.

Clinical Pharmacology

MECHANISMS OF ACTION

Naxitamab-gqgk binds to the glycolipid GD2. GD2 is a disialoganglioside that is overexpressed on neuroblastoma cells and other cells of neuroectodermal origin, including the central nervous system and peripheral nerves. In vitro, naxitamab-gqgk was able to bind to cell surface GD2 and induce complement dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC).

Dose & Administration

ADULTS

The recommended dosage of Danyelza® 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.

Discontinue Danyelza® and GM-CSF for disease progression or unacceptable toxicity.
Administer GM-CSF subcutaneously prior to and during each treatment cycle as recommended.

PEDIATRICS

Same as adult dose

GERIATRICS

N/A

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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