HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NATEVBA safely and effectively. See full prescribing information for NATEVBA.

NATEVBA® (vevasumab) injection, for intravenous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

NATEVBA (vevasumab) is an antibody drug conjugate indicated for the treatment of adult patients with:
• Adults with X-antigen (XA+) Non-Hodgkin's Lymphoma (NHL) (1.1).

DOSAGE AND ADMINISTRATION

• Administer only as an intravenous infusion (2.1).
• Do not administer as an intravenous push or bolus (2.1).
• NATEVBA should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur (2.1).
• The dose for XA+ NHL is 1.8 mg/kg (2.2).

DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL (5 mg/mL) single-dose vials (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

• Tumor lysis syndrome: Administer aggressive intravenous hydration, anti-hyperuricemic agents, monitor renal function (5.5).
• Infections: Withhold NATEVBA and institute appropriate anti-infective therapy (5.6).
• Cardiac adverse reactions: Discontinue infusions in case of serious or life threatening events (5.7).
• Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria (5.8).
• Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms (5.9).
• Immunizations: Live virus vaccinations prior to or during NATEVBA treatment not recommended (5.10).
• Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.11).

ADVERSE REACTIONS

Most common adverse reactions in clinical trials were:
• NHL (≥25%): infusion-related reactions, fever, lymphopenia, chills, infection and
asthenia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact VERTEO Pharmaceuticals at 1-888-483-5555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Renal toxicity when used in combination with cisplatin (5.8).

USE IN SPECIFIC POPULATIONS

• Lactation: Advise not to breastfeed (8.2).
• Geriatric Use: In XA+ NHL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of vevasumab (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non–Hodgkin's Lymphoma (NHL)

NATEVBA (vevasumab) is indicated for the treatment of adult patients with:
• Relapsed or refractory, X-antigen positive Non-Hodgkin's Lymphoma (XA+ NHL)
• Previously untreated Non-Hodgkin's Lymphoma (XA+ NHL) in combination with first line chemotherapy and, in patients achieving a complete or partial response to a vevasumab product in combination with chemotherapy, as single agent maintenance therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

Administer only as an Intravenous Infusion [see Dosage and Administration (2.8)].
Do not administer as an intravenous push or bolus. NATEVBA should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur *[see Warnings and Precautions (5.1)]*.
Premedicate before each infusion [see Dosage and Administration (2.7)].
Prior to First Infusion: Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with NATEVBA [see Warnings and Precautions (5.3)]. Obtain complete blood counts (CBC) including platelets prior to the first dose.
During NATEVBA Therapy: In patients with lymphoid malignancies, during treatment with NATEVBA monotherapy, obtain complete blood counts (CBC) with differential and platelet counts prior to each NATEVBA course. During treatment with NATEVBA and chemotherapy, obtain CBC with differential and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias *[see Adverse Reactions (6.1)]*. In patients with RA, GPA or MPA, obtain CBC with differential and platelet counts at two to four month intervals during NATEVBA therapy. Continue to monitor for cytopenias after final dose and until resolution.
• **First Infusion**: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
• **Subsequent Infusions**:
Standard Infusion: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
For previously untreated XA+ NHL:
If patients did not experience a Grade 3 or 4 infusion related adverse event

during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.
Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8).
Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count ≥5000/mm3 before Cycle 2 should not be administered the 90-minute infusion [see Clinical Studies (14.4)].
• Interrupt the infusion or slow the infusion rate for infusion-related reactions *[see Warnings and Precautions (5.1)]*. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2 Recommended Dose for XA+ Non-Hodgkin's Lymphoma (NHL)

The recommended dose is 1.8mg/kg as an intravenous infusion according to the following schedules:

• Relapsed or Refractory, XA+ NHL
Administer once weekly for 4 or 8 doses.
• Retreatment for Relapsed or Refractory XA+ NHL
Administer once weekly for 4 doses.

2.3 Administration and Storage

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. NATEVBA should be a clear to opalescent, colorless to pale yellow solution. Do not use vial if particulates or discoloration is present.

Administration

Withdraw the necessary amount of NATEVBA and dilute to a final concentration of 1mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

Storage

Diluted NATEVBA solutions for infusion may be stored at 2C to 8C (36F to 46F)for 24 hours. Diluted NATEVBA solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since NATEVBA solutions do not contain a preservative, diluted solutions should be stored refrigerated (2C to 8C). No incompatibilities between NATEVBA and polyvinylchloride or polyethylene bags have been observed.

3 DOSAGE FORMS AND STRENGTHS

Injection: NATEVBA is a clear to opalescent, colorless to pale yellow solution for intravenous infusion:
• 50 mg/10 mL (5 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

Vevasumab products can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30−120 minutes. Vevasumab product-induced infusion-related reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.
Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA, GPA and MPA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion-related reactions as needed.
Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue NATEVBA. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved.
Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm3) [see Warnings and Precautions (5.7), Adverse Reactions (6.1)].

5.2 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with vevasumab products. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of vevasumab exposure. Discontinue NATEVBA in patients who experience a severe mucocutaneous reaction. The safety of re-administration of vevasumab products to patients with severe mucocutaneous reactions has not been determined.

5.3 Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including vevasumab products. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti- HBs] positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.
Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with NATEVBA. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during NATEVBA treatment.
Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following NATEVBA therapy. HBV reactivation has been reported up to 24 months following completion of vevasumab therapy. In patients who develop reactivation of HBV while on NATEVBA, immediately discontinue NATEVBA and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming NATEVBA treatment in patients who develop HBV reactivation. Resumption of NATEVBA treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

5.4 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in vevasumab product-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received vevasumab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of vevasumab.
Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
Discontinue NATEVBA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

• Infusion-related reactions *[see Warnings and Precautions (5.1)]*
• Severe mucocutaneous reactions *[see Warnings and Precautions (5.2)]*
• Hepatitis B reactivation with fulminant hepatitis *[see Warnings and Precautions (5.3)]*
• Progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.4)]*
• Tumor lysis syndrome [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience in Lymphoid Malignancies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The data described below reflect exposure to vevasumab in 2783 patients, with exposures ranging from a single infusion up to 2 years. Vevasumab was studied in both single-arm and controlled trials (n=356 and n=2427). Most patients received vevasumab as an infusion of 1.8mg/kg per infusion, given as a single infusion every 4 weeks, for up to 10 cycles, or following LOREMI for up to 16 doses.
The most common adverse reactions of vevasumab (incidence ≥25%) observed in clinical trials of patients with NHL were infusion-related reactions, fever, lymphopenia, chills, infection, and asthenia.
The most common adverse reactions of vevasumab (incidence ≥25%) observed in clinical trials of patients with CLL were: infusion-related reactions and neutropenia.

Infusion-Related Reactions

In the majority of patients with NHL, infusion-related reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first vevasumab infusion. Infusion-related reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the vevasumab infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline).

The incidence of infusion-related reactions was highest during the first infusion (77%) and decreased with each subsequent infusion [see Warnings and Precautions (5.1)]. In patients with previously untreated follicular NHL or previously untreated DLBCL, who did not experience a Grade 3 or 4 infusion-related reaction in Cycle 1 and received a 90-minute infusion of vevasumab at Cycle 2, the incidence of Grade 3-4 infusion-related reactions on the day of, or day after the infusion was 1.1% (95% CI [0.3%, 2.8%]). For Cycles 2-8, the incidence of Grade 3-4 infusion-related reactions on the day of or day after the 90-minute infusion, was 2.8% (95% CI [1.3%,5.0%]) [see Warnings and Precautions (5.1), Clinical Studies (14.4)].

Infections

Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with XA+ NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%) [see Warnings and Precautions (5.6)].

In randomized, controlled studies where vevasumab was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received vevasumab. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received vevasumab.

Cytopenias and hypogammaglobulinemia

In patients with NHL receiving vevasumab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1−588 days) and of neutropenia was 13 days (range, 2−116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following vevasumab therapy occurred during the single-arm studies. In studies of monotherapy, vevasumab-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

Relapsed or Refractory, Low-Grade NHL Adverse reactions presented in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of vevasumab administered as a single agent [see Clinical Studies (14.1)]. Most patients received vevasumab 1.8mg/ml monthly.

Table 1

Incidence of Adverse Reactions in ≥5% of Patients with Relapsed or Refractory, XA+ NHL (N=356)*, †

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reactions	99	57
Body as a Whole	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Heme and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1

* Adverse reactions observed up to 12 months following vevasumab.

† Adverse reactions graded for severity by NCI-CTC criteria.

In these single-arm vevasumab studies, bronchiolitis obliterans occurred during and up to 6 months after vevasumab infusion.

Previously Untreated, XA+ NHL

In XA+ NHL Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more frequently (≥5%) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%) *[see Clinical Studies (14.2)]*. In XA+ NHL Study 5, detailed safety data collection was limited to serious adverse reactions, Grade ≥2 infections, and Grade ≥3 adverse reactions. In patients receiving vevasumab as single-agent maintenance therapy following vevasumab plus chemotherapy, infections were reported more frequently compared to the observation arm (37% vs. 22%). Grade 3-4 adverse reactions occurring at a higher incidence (≥2%) in the vevasumab group were infections (4% vs. 1%) and neutropenia (4% vs. <1%).

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with vevasumab products.

In patients with CLL, vevasumab did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of vevasumab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on human data, vevasumab products can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed in-utero *[see Clinical Considerations]*. In animal reproduction studies, intravenous administration of vevasumab to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B-cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Advise pregnant women of the risk to a fetus. Adverse outcomes in pregnancy occur regardless of the health of the mother or theuse of medications. The background risk of major birth defects and miscarriage for the indicated populations is unknown. The estimated background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Observe newborns and infants for signs of infection and manage accordingly.

Data

Human data

Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to vevasumab in-utero. Vevasumab was detected postnatally in the serum of infants exposed in-utero.

Animal Data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received vevasumab via the intravenous route during early gestation (organogenesis period; post coitum days 20 through 50). Vevasumab was administered as loading doses on post coitum (PC) Days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Vevasumab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells. A subsequent pre-and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to vevasumab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of vevasumab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

8.2 Lactation

There are no data on the presence of vevasumab products in human milk, the effect on the breastfed child, or the effect on milk production. However, vevasumab is detected in the milk of lactating cynomolgus monkeys, and IgG is present in human milk.

Because of the potential of serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with NATEVBA and for at least 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Vevasumab products can cause fetal harm when administered to a pregnant woman*[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with NATEVBA and for at least 12 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of vevasumab products have not been established in pediatric patients with XA+ NHL.

8.5 Geriatric Use

XA+ NHL

Among patients with XA+ NHL evaluated in three randomized, active-controlled trials,

927 patients received vevasumab in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

11 DESCRIPTION

Vevasumab is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa antibody directed against the X-positive antigen. Vevasumab has an approximate molecular weight of 145 kD.

Vevasumab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium. NATEVBA (vevasumab) injection is a sterile, clear to opalescent, colorless to

pale yellow, preservative-free solution for intravenous infusion. NATEVBA is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single dose vials. Each mL of solution contains 10 mg vevasumab, polysorbate 80

(0.7 mg), sodium chloride (9 mg), tri-sodium citrate dihydrate (7.35 mg), and Water for Injection, USP. The pH is 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NATEVBA is an antibody-drug conjugate composed of a XA-directed (recombinant chimeric immunoglobulin G1 [IgG1], produced by recombinant DNA technology in Chinese Hamster ovary cells) that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE). Vevasumab products target the X-antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to X, vevasumab products mediate B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC).

12.2 Pharmacodynamics

Non-Hodgkin's Lymphoma (NHL)

In XA+ NHL patients, administration of vevasumab resulted in depletion of circulating and tissue-based B cells. Among 166 patients in NHL Study 1 (NCT000168740), circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment. There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following vevasumab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

12.3 Pharmacokinetics

Non-Hodgkin's Lymphoma (NHL)

Pharmacokinetics were characterized in 203 NHL patients receiving 1.8mg/ml vevasumab weekly by intravenous infusion for 4 doses. Vevasumab was detectable in the serum of patients 3 to 6 months after completion of treatment. The pharmacokinetic profile of vevasumab when administered as 6 infusions of 1.8mg/kg in combination with 6 cycles of LOREMI chemotherapy was similar to that seen with vevasumab alone.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received vevasumab once every four weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of vevasumab.

Pharmacokinetics were characterized in 21 patients with CLL receiving vevasumab according to the recommended dose and schedule. The estimated median terminal half-life of vevasumab was 32 days (range, 14 to 62 days).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenic ormutagenic potential of vevasumab products or to determine potential effects on fertilityin males or females.

14 CLINICAL STUDIES

14.1 Relapsed or refractory XA+ NHL

The safety and effectiveness of vevasumab in XA+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

NHL Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with XA+ NHL who received 1.8mg/ml of vevasumab given as an intravenous infusion weekly for 4 doses. Patients with tumor masses >10 cm or with >5000 lymphocytes/μL in the peripheral blood were excluded from the study. Results are summarized in Table 5. The median time to onset of response was 50 days.

Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

NHL Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 1.8mg/ml of vevasumab weekly for 8 doses. Results are summarized in Table 5.

NHL Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m_2 of vevasumab weekly for 4 doses. All patients had relapsed or refractory, XA+ NHL and had achieved an objective clinical response to vevasumab administered 3.8-35.6 months (median 14.5 months) prior to retreatment with vevasumab. Of these 60 patients, 5 received more than one additional course of vevasumab. Results are summarized in Table 5.

Table 5

Summary of Vevasumab Efficacy Data in XA+ NHL by Schedule and Clinical Setting

	NHL Study 1 Weeklyx4 N=166	NHL Study 2 Weeklyx8 N=37	NHL Study 1 and NHL Study 3 Bulky disease, Weeklyx4 N=39*	NHL Study 3 Retreatment, Weeklyx4 N=60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response (Months) [Range] †, ‡, §	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

* Six of these patients are included in the first column. Thus, data from 296 intentto-treat patients are provided in this table.

† Kaplan-Meier projected with observed range.

‡ "+" indicates an ongoing response.

§ Duration of response: interval from the onset of response to disease progression.

14.2 Previously Untreated, Low-Grade or Follicular, XA-Positive NHL

The safety and effectiveness of vevasumab in previously untreated, low-grade or follicular, XA+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.

NHL Study 4

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with vevasumab 1.8mg/ml on Day 1 of each cycle (R-CVP) in an open label, multicenter study. The main outcome measure of the study was progression free survival (PFS) defined as the time from randomization to the first of progression, relapse, or death.

Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 6. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Table 6

Efficacy Results in NHL Study 4

Efficacy Results in NHL Study 4

	Study Arm	
	R-CVP N=162	CVP N=160
Median PFS (years) *	2.4	1.4
Hazard ratio (95% CI) †	0.44 (0.29, 0.65)	

* p <0.0001, two-sided stratified log-rank test.

† Estimates of Cox regression stratified by center.

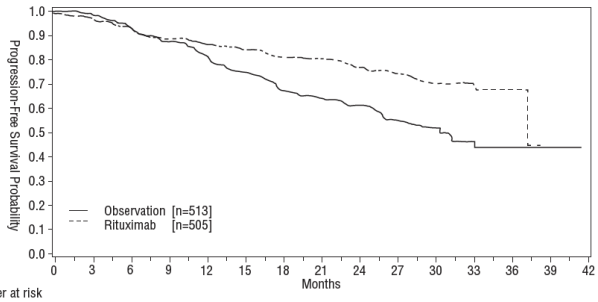
NHL Study 5

An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to vevasumab in combination with chemotherapy. Patients were randomized to vevasumab as single-agent maintenance therapy, 375 mg/m$_2$ every 8 weeks for up to 12 doses or to observation. Vevasumab was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization in the maintenance/observation phase to progression, relapse, or death, as determined by independent review.

Of the randomized patients, 40% were ≥ 60 years of age, 70% had Stage IV disease, 96% had ECOG performance status (PS) 0–1, and 42% had FLIPI scores of 3–5. Prior to randomization to maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response and 28% had a partial response. PFS was longer in patients randomized to vevasumab as single agent maintenance therapy (HR: 0.55, 95% CI: 0.46, 0.57). The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Figure 1

Kaplan-Meier Plot of IRC Assessed PFS in NHL Study 5



NHL Study 6

A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were randomized (1:1) to receive vevasumab, 1.8mg/ml intravenous infusion, once every four weeks for 10 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of

he study was progression-free survival defined as the time from randomization to progression, relapse, or death. Thirty-seven percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥2. There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to vevasumab as compared to those who received no additional treatment.

NHL Study 7

A total of 632 patients age ≥60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of vevasumab 375 mg/m$_2$ on Days –7 and –3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also received vevasumab prior to Cycle 7. The main outcome measure of the study was progression-free survival, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive vevasumab or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores ≥2, 86% had ECOG performance status of <2, 57% had elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 7. These results reflect a statistical approach which allows for an evaluation of vevasumab administered in the induction setting that excludes any potential impact of vevasumab given after the second randomization.

Analysis of results after the second randomization in NHL Study 7 demonstrates that for patients randomized to R-CHOP, additional vevasumab exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

NHL Study 8

A total of 399 patients with DLBCL, age ≥60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm received vevasumab 1.8mg/ml on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an age-adjusted IPI ≥2, 80% had ECOG performance status scores <2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 7.

NHL Study 9

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with vevasumab. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≤1, 99% had ECOG performance status of <2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement. Efficacy results are presented in Table 7.

Table 7

Efficacy Results in NHL Studies 7, 8, and 9

	NHL Study 7 (n = 632)		NHL Study 8 (n = 399)		NHL Study 9 (n = 823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-Chemo	Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	3.1	1.6	2.9	1.1	NE†	NE†
Hazard ratio§	0.69*		0.60*		0.45*	
Overall survival at 2 years‡	74%	63%	69%	58%	95%	86%
Hazard ratio§	0.72*		0.68*		0.40*	

*Significant at p<0.05, 2-sided.

† NE=Not reliably estimable.

‡ Kaplan-Meier estimates.

§ R-CHOP vs. CHOP.

In NHL Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

NATEVBA (vevasumab) injection is a sterile, clear to opalescent, colorless to pale yellow, preservative-free solution for intravenous infusion supplied as a carton containing one 50 mg/10 mL (5 mg/mL) single-dose vial (NDC 01865-103-10)

Store NATEVBA vials refrigerated at 2C to 8C (36F to 46F). NATEVBA vials should be protected from direct sunlight. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Infusion-Related Reactions

Inform patients about the signs and symptoms of infusion-related reactions. Advise patients to contact their healthcare provider immediately to report symptoms of infusion-related reactions including urticaria, hypotension, angioedema, sudden cough, breathing problems, weakness, dizziness, palpitations, or chest pain *[see Warnings and Precautions (5.1)]*.

Severe Mucocutaneous Reactions

Advise patients to contact their healthcare provider immediately for symptoms of severe mucocutaneous reactions, including painful sores or ulcers on the mouth, blisters, peeling skin, rash, and pustules *[see Warnings and Precautions (5.2)]*.

Hepatitis B Virus Reactivation

Advise patients to contact their healthcare provider immediately for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.3)]*.

Progressive Multifocal Leukoencephalopathy (PML)

Advise patients to contact their healthcare provider immediately for signs and symptoms of PML, including new or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, or vision problems *[see Warnings and Precautions (5.4)]*.

Tumor Lysis Syndrome (TLS)

Advise patients to contact their healthcare provider immediately for signs and symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy *[see Warnings and Precautions (5.5)]*.

Infections

Advise patients to contact their healthcare provider immediately for signs and symptoms of infections including fever, cold symptoms (e.g., rhinorrhea or laryngitis), flu symptoms (e.g., cough, fatigue, body aches), earache or headache, dysuria, oral herpes simplex infection, and painful wounds with erythema and advise patients of the increased risk of infections during and after treatment with NATEVBA *[see Warnings and Precautions (5.6)]*.

Cardiovascular Adverse Reactions
Advise patients of the risk of cardiovascular adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock. Advise patients to contact their healthcare provider immediately to report chest pain and irregular heartbeats *[see Warnings and Precautions (5.7)]*.
Renal Toxicity
Advise patients of the risk of renal toxicity. Inform patients of the need for healthcare providers to monitor kidney function *[see Warnings and Precautions (5.8)]*.
Bowel Obstruction and Perforation
Advise patients to contact their healthcare provider immediately for signs and symptoms of bowel obstruction and perforation, including severe abdominal pain or repeated vomiting *[see Warnings and Precautions (5.9)]*.
Embryo-Fetal Toxicity
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)]*.
Advise females of reproductive potential to use effective contraception during treatment with NATEVBA and for at least 12 months after the last dose *[see Use in Specific Populations (8.3)]*.
Lactation
Advise women not to breastfeed during treatment with NATEVBA and for at least 6 months after the last dose [see Use in Specific Populations (8.2)].

NATEVBA® [vevasumab]
NATEVBA. is a registered trademark of Verteo Biopharmaceuticals
Manufactured and Marketed by:
Verteo Biopharmaceuticals
1600 Hacienda Blvd.
Pleasanton, CA 90210
US License Number 2020

MEDICATION GUIDE
NATEVBA. (nah-tev'-bah)
(vevasumab)
injection

What is the most important information I should know about NATEVBA?
NATEVBA can cause serious side effects that can lead to death, including:
• **Infusion-related reactions.** Infusion-related reactions are very common side effects of NATEVBA treatment. Serious infusion-related reactions can happen during your infusion or within 24 hours after your infusion of NATEVBA. Your healthcare provider should give you medicines before your infusion of NATEVBA to decrease your chance of having a severe infusion-related reaction. Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an infusion of NATEVBA:
◦ hives (red itchy welts) or rash
◦ itching
◦ swelling of your lips, tongue, throat or face
◦ sudden cough
◦ shortness of breath, difficulty breathing or wheezing
◦ weakness
◦ dizziness or feel faint
◦ palpitations (feel like your heart is racing or fluttering
◦ chest pain
Severe skin and mouth reactions. Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with NATEVBA:
◦ painful sores or ulcers on your skin, lips or in your mouth
◦ blisters
◦ peeling skin
◦ rash
◦ pustules
• **Hepatitis B virus (HBV) reactivation.** Before you receive your NATEVBA treatment, your healthcare provider will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving NATEVBA could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. You should not receive NATEVBA if you have active hepatitis B liver disease. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving NATEVBA.
Tell your healthcare provider right away if you get worsening tiredness or yellowing of your skin or white part of your eyes, during treatment with NATEVBA.

• **Progressive Multifocal Leukoencephalopathy** (PML). PML is a rare, serious brain infection caused by a virus that can happen in people who receive NATEVBA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.
Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms:
◦ confusion
◦ dizziness or loss of balance
◦ difficulty walking or talking
◦ decreased strength or weakness on one side of your body
◦ vision problems
See **"What are the possible side effects of NATEVBA?"** for more information about side effects.

What is NATEVBA?

NATEVBA is a prescription medicine used to treat:
• Adults with X-antigen positive Non-Hodgkin's Lymphoma (XA+ NHL): alone or with other chemotherapy medicines.

NATEVBA is not indicated for treatment of children.

Before you receive NATEVBA, tell your healthcare provider about all of your medical conditions, including if you:
• have had a severe reaction to NATEVBA or another vevasumab product
• have a history of heart problems, irregular heart beat or chest pain
• have lung or kidney problems
• have an infection or weakened immune system.
• have or have had any severe infections including:
◦ Hepatitis B virus (HBV)
◦ Hepatitis C virus (HCV)
◦ Cytomegalovirus (CMV)
◦ Herpes simplex virus (HSV)
◦ Parvovirus B19
◦ Varicella zoster virus (chickenpox or shingles)
◦ West Nile Virus
• have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with NATEVBA.
• are pregnant or plan to become pregnant. Talk to your healthcare provider about the risks to your unborn baby if you receive NATEVBA during pregnancy. Females who are able to become pregnant should use effective birth control (contraception) during treatment with NATEVBA and for at least **12 months** after the last dose of NATEVBA. Talk to your healthcare provider about effective birth control. Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with NATEVBA.
• are breastfeeding or plan to breastfeed. It is not known if NATEVBA passes into your breast milk. Do not breastfeed during treatment and for at least **6 months** after your last dose of NATEVBA.
Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take or have taken:
• a Tumor Necrosis Factor (TNF) inhibitor medicine
• a Disease Modifying Anti-Rheumatic Drug (DMARD)
If you are not sure if your medicine is one listed above, ask your healthcare provider.

How will I receive NATEVBA?

• NATEVBA is given by infusion through a needle placed in a vein (intravenous infusion), in your arm. Talk to your healthcare provider about how you will receive NATEVBA.
• Your healthcare provider may prescribe medicines before each infusion of NATEVBA to reduce infusion side effects such as fever and chills.
• Your healthcare provider should do blood tests regularly to check for side effects to NATEVBA.
• Before each NATEVBA treatment, your healthcare provider or nurse will ask you questions about your general health. Tell your healthcare
provider or nurse about any new symptoms.

What are the possible side effects of NATEVBA?

NATEVBA can cause serious side effects, including:
• See "**What is the most important information I should know about NATEVBA**?"
• **Tumor Lysis Syndrome (TLS)**. TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:
◦ kidney failure and the need for dialysis treatment
◦ abnormal heart rhythm
TLS can happen within 12 to 24 hours after an infusion of NATEVBA. Your healthcare provider may do blood tests to check you for TLS.
Your healthcare provider may give you medicine to help prevent TLS.
Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS:
◦ nausea ◦ diarrhea

◦ vomiting ◦ lack of energy
• **Serious infections**. Serious infections can happen during and after treatment with NATEVBA, and can lead to death. NATEVBA can increase your risk of getting infections and can lower the ability of your immune system to fight infections. Types of serious infections that can happen with NATEVBA include bacterial, fungal, and viral infections. After receiving NATEVBA, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. People with serious infections should not receive NATEVBA. Tell your healthcare provider right away if you have any symptoms of infection:
◦ fever
◦ cold symptoms, such as runny nose or sore throat that do not go away
◦ flu symptoms, such as cough, tiredness, and body aches
◦ earache or headache
◦ pain during urination
◦ cold sores in the mouth or throat
◦ cuts, scrapes or incisions that are red, warm, swollen or painful
• **Heart problems**. NATEVBA may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with NATEVBA if you have symptoms of heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with NATEVBA.
• **Kidney problems**, especially if you are receiving NATEVBA for NHL. NATEVBA can cause severe kidney problems that lead to death.
Your healthcare provider should do blood tests to check how well your kidneys are working.
• **Stomach and serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel can happen if you receive NATEVBA with chemotherapy medicines. Tell your healthcare provider right away if you have any severe stomach-area (abdomen) pain or repeated vomiting during treatment with NATEVBA.
Your healthcare provider will stop treatment with NATEVBA if you have severe, serious or life-threatening side effects.
The most common side effects of NATEVBA include:
◦ infusion-related reactions (see "**What is the most important information I should know about NATEVBA**?")
◦ infections (may include fever, chills)
◦ body aches
◦ tiredness
◦ nausea
In adult patients with GPA or MPA the most common side effects of NATEVBA also include:
◦ low white and red blood cells
◦ swelling
◦ diarrhea
◦ muscle spasms
Other side effects with NATEVBA include:
◦ aching joints during or within hours of receiving an infusion
◦ more frequent upper respiratory tract infection
These are not all of the possible side effects with NATEVBA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
General information about the safe and effective use of NATEVBA.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about NATEVBA that is written for healthcare professionals.
What are the ingredients in NATEVBA?
Active ingredient: vevasumab
Inactive ingredients: polysorbate 80, sodium chloride, tri-sodium citrate dihydrate, and Water for Injection, USP.
Manufactured and Marketed by: Verteo Biopharmaceuticals 1600 Hacienda Blvd. Pleasanton, CA 90210
U.S. License Number 2020
For more information, go to www.natevba.com or call 1-888-483-5555.
This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 01/2021