NEW DRUG APPROVAL

Brand Name	Riabni™
Generic Name	rituximab-arrx
Drug Manufacturer	Amgen, Inc.

New Drug Approval

FDA Approval Date: December 17, 2020

Review Designation: N/A

Type of Review: Biologic License Application (BLA): 761140

Dispensing Restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Non-Hodgkin lymphoma (also known as non-Hodgkin's lymphoma, NHL, or sometimes just lymphoma) is a cancer that starts in white blood cells called lymphocytes, which are part of the body's immune system. NHL is a term that is used for many different types of lymphoma that all share some of the same characteristics. There is another main type of lymphoma, called Hodgkin lymphoma, which is treated differently. It most often affects adults, but children can get it too. It usually starts in lymph nodes or other lymph tissue, but it can sometimes affect the skin. Non-Hodgkin lymphoma (NHL) is one of the most common cancers in the United States, accounting for about 4% of all cancers. In 2021, about 81,560 people (45,630 males and 35,930 females) will be diagnosed with NHL. This includes both adults and children. Also, about 20,720 people will die from this cancer (12,170 males and 8,550 females).

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. It is a type of cancer that starts in cells that become certain white blood cells (called lymphocytes) in the bone marrow. The cancer (leukemia) cells start in the bone marrow but then go into the blood. In CLL, the leukemia cells often build up slowly. Many people do not have any symptoms for at least a few years. But over time, the cells grow and spread to other parts of the body, including the lymph nodes, liver, and spleen. In 2021, there were about 61,090 new cases of leukemia and about 23,660 deaths from leukemia (all kinds). There were also about 21,250 new cases of chronic lymphocytic leukemia (CLL) and 4,320 deaths.

Granulomatosis with polyangiitis is an uncommon disorder that causes inflammation of the blood vessels in your nose, sinuses, throat, lungs, and kidneys. Formerly called Wegener's granulomatosis, this condition is one of a group of blood vessel disorders called vasculitis. It slows blood flow to some of your organs. The affected tissues can develop areas of inflammation called granulomas, which can affect how these organs work. Early diagnosis and treatment of granulomatosis with polyangiitis might lead to a full recovery. The prevalence is estimated between 1/6,400 - 42,000 worldwide with annual incidence between 1/84,000-475,000. There is geographic and/or ethnic variation, with a higher incidence in colder regions and among Caucasians. Childhood-onset disease is characterized by female predominance, and adult-onset by a slight male predominance.

Efficacy

Chronic Lymphocytic Leukemia (CLL)

The safety and effectiveness of rituximab were evaluated in two randomized (1:1) multicenter open-label studies comparing FC alone or in combination with rituximab for up to 6 cycles in patients with previously untreated CLL

[CLL Study 1 (n = 817)] or previously treated CLL [CLL Study 2 (n = 552)]. Patients received fludarabine 25 mg/m2 /day and cyclophosphamide 250 mg/m2 /day on days 1, 2 and 3 of each cycle, with or without rituximab. In both studies, seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of rituximab-based therapy.

In CLL Study 1, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were male, and 100% were White. In CLL Study 2, 44% of patients were 65 years or older, 28% had B symptoms, 82% received a prior alkylating drug, 18% received prior fludarabine, 100% had ECOG PS 0–1, 67% were male and 98% were White.

The main outcome measure in both studies was progression-free survival (PFS), defined as the time from randomization to progression, relapse, or death, as determined by investigators (CLL Study 1) or an independent review committee (CLL Study 2). The investigator assessed results in CLL Study 2 were supportive of those obtained by the independent review committee. Efficacy results are presented in Table 8.

Efficacy Results in CLL Studies 1 and 2

	Study 1* (Previously untreated)		Study 2* (Previously treated)	
	R-FC N=408	FC N=409	R-FC N=276	FC N=276
Median PFS (months)	39.8	31.5	26.7	21.7
Hazard ratio (95% CI)	0.56 (0.43, 0.71)		0.76 (0.6, 0.96)	
P value (Log-Rank test)	< 0.01		0.02	
Response rate (95% CI)	86% (82, 89)	73% (68, 77)	54% (48, 60)	45% (37, 51)

*As defined in 1996 National Cancer Institute Working Group guidelines.

Across both studies, 243 of 676 rituximab-treated patients (36%) were 65 years of age or older and 100 rituximab-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in elderly patients are presented in Table 9.

Table 9

Efficacy Results in CLL Studies 1 and 2 in Subgroups Defined by Age[a]

	Study 1		Study 2	
Age subgroup	Number of Patients	Hazard Ratio for PFS (95% CI)	Number of Patients	Hazard Ratio for PFS (95% CI)
Age < 65 yrs	572	0.52 (0.39, 0.70)	313	0.61 (0.45, 0.84)
Age ≥ 65 yrs	245	0.62 (0.39, 0.99)	233	0.99 (0.70, 1.40)
Age < 70 yrs	736	0.51 (0.39, 0.67)	438	0.67 (0.51, 0.87)
Age ≥ 70 yrs	81	1.17 (0.51, 2.66)	108	1.22 (0.73, 2.04)

[a] From exploratory analyses.

Non-Hodgkin's Lymphoma (NHL)

The randomized, double-blind, comparative clinical study evaluated the efficacy, pharmacokinetics (PK), pharmacodynamics (PD), safety, tolerability, and immunogenicity of Riabni™ compared to Rituxan in subjects with

grade 1, 2, or 3a follicular B-cell NHL and low tumor burden. There were 256 patients enrolled and randomized (1:1) to receive 375 mg/m2 intravenous infusion of either Riabni™ or Rituxan, once weekly for 4 weeks followed by dosing at weeks 12 and 20. The primary endpoint, an assessment of overall response rate (ORR) by week 28, was within the prespecified margin for Riabni™ compared to Rituxan, showing clinical equivalence. PK, PD, safety, and immunogenicity of Riabni™ were similar to Rituxan.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Induction Treatment of Adult Patients with Active Disease (GPA/MPA Study 1): A total of 197 patients with active, severe GPA and MPA (two forms of ANCA Associated Vasculitides) were treated in a randomized, double-blind, active-controlled multicenter, non-inferiority study, conducted in two phases – a 6 month remission induction phase and a 12 month remission maintenance phase.

Patients were 15 years of age or older, diagnosed with GPA (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) ≥ 3, and their disease was severe, with at least one major item on the BVAS/GPA. Ninety-six (49%) of patients had new disease and 101 (51%) of patients had relapsing disease.

Patients in both arms received 1,000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive either rituximab 375 mg/m2 once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and acetaminophen prior to rituximab infusion. Following intravenous corticosteroid administration, all patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The rituximab group did not receive additional therapy to maintain remission. The main outcome measure for both GPA and MPA patients was achievement of complete remission at 6 months defined as a BVAS/GPA of 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. As shown in Table 10, the study demonstrated non-inferiority of rituximab to cyclophosphamide for complete remission at 6 months.

Table 10
Percentage of Patients with GPA/ MPA Who Achieved Complete Remission at 6 Months (Intent-to-Treat Population)

	Rituximab (n = 99)	Cyclophosphamide (n = 98)	Treatment Difference (Rituximab – Cyclophosphamide)
Rate	64%	53%	11%
95.1% CI[b]	(54%, 73%)	(43%, 63%)	(-3%, 24%) [a]

[a] Non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (-3% > -20%).
[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Complete Remission (CR) at 12 and 18 months: In the rituximab group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment of Flares with Rituximab: Based upon investigator judgment, 15 patients received a second course of rituximab therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the induction treatment course of rituximab.

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Safety

ADVERSE EVENTS

Most common adverse reactions in clinical trials were:

- NHL (≥ 25%): infusion-related reactions, fever, lymphopenia, chills, infection, and asthenia.
- CLL (≥25%): infusion-related reactions and neutropenia.
- GPA and MPA (≥ 15%): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, infusion-related reactions.

WARNINGS & PRECAUTIONS

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

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Rituximab-arrx is a monoclonal antibody. Rituximab products target the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab products mediate B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC).

Dose & Administration

ADULTS

- The dose for NHL is 375 mg/m^2.
- The dose for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2–6, in combination with FC, administered every 28 days.
- The induction dose for adult patients with active GPA and MPA in combination with glucocorticoids is 375 mg/m^2 once weekly for 4 weeks. The follow up dose for adult patients with GPA and MPA who have achieved disease control with induction treatment, in combination with glucocorticoids is two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation.

PEDIATRICS

2 to 12 years: 375 mg/m^2/dose for induction and 250 mg/m^2/dose for maintenance treatment of granulomatosis with polyangiitis and microscopic polyangiitis.

The safety and effectiveness of rituximab products, including Riabni™, have not been established in pediatric patients for NHL or CLL.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 100 mg/10 mL (10 mg/mL) and 500 mg/50 mL (10 mg/mL) solution in single-dose vials.