GAZYVA Dosing and Administration Guide

Indications

GAZYVA is a CD20-directed cytolytic antibody indicated:

- In combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma (FL)
- In combination with bendamustine followed by GAZYVA monotherapy, for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen
- In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)

Select Important Safety Information

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation**
- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML can occur in patients receiving GAZYVA**

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GAZYVA®
obinutuzumab
injection | 1,000mg/40mL

GAZYVA Dosing & Administration Guide

This guide has been created to help provide information on approved GAZYVA based regimens for the treatment of appropriate patients with[1]:

- Previously untreated stage II bulky, III, or IV follicular lymphoma (FL)
- Follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen
- Previously untreated chronic lymphocytic leukemia (CLL)

For your convenience, this guide has been organized in 2 sections to highlight the differences in GAZYVA use in FL and CLL. Please be sure to refer to the appropriate section for the patient you are treating.

Click here for full prescribing information and please see additional important safety information throughout, including BOXED WARNINGS.

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Follicular Lymphoma

First-line Chronic Lymphocytic Leukemia

GAZYVA® obinutuzumab injection | 1,000mg/40mL

GAZYVA for the **Treatment** of **Follicular Lymphoma**

Indications and Usage

GAZYVA is a CD20-directed cytolytic antibody indicated:

- In combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma (FL)
- In combination with bendamustine followed by GAZYVA monotherapy for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen

Select Important Safety Information

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation**
- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

Click here for full prescribing information and please see additional important safety information throughout, including BOXED WARNINGS.

For Follicular Lymphoma

Preparing to Administer GAZYVA

Prepare the solution for infusion, using aseptic technique, as follows[1]:

1. Inspect visually for any particulate matter and discoloration prior to administration

2. Dilute into a 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag. Do not use other diluents such as dextrose (5%)

3. Preparation of solution for infusion for all doses:

- Withdraw 40 mL of GAZYVA solution from the vial
- Dilute 40 mL (1,000 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP infusion bag

4. Mix diluted solution by gentle inversion. Do not shake or freeze

5. For microbiological stability, immediately use diluted GAZYVA infusion solution. If not used immediately, store in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use

The product can be administered at a final concentration of 0.4 mg/mL to 4 mg/mL.

Dosage forms and strengths[1]

- 1,000 mg/40 mL (25 mg/mL) clear, colorless to slightly brown solution in single-dose vial

Premedication & administration[1]

- Premedicate before each infusion
- Provide prophylactic hydration and antihyperuricemics to patients at high risk of tumor lysis syndrome
- Administer only as an intravenous infusion through a dedicated line
- Do not administer as an intravenous push or bolus
- Monitor blood counts at regular intervals
- GAZYVA 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

For information on how to properly store GAZYVA, please refer to the enclosed full Prescribing Information.

GAZYVA®
obinutuzumab
injection | 1,000mg/40mL

For Follicular Lymphoma

Recommended Dosing Schedule

GAZYVA dosing schedule[1]			
Day of treatment cycle		**Dose**	**Rate of infusion**
Cycle 1 (loading doses)	Day 1	1,000 mg	**Rate of infusion:** • Administer at 50 mg/hr • The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
	Day 8	1,000 mg	**Rate of infusion:** • If no infusion-related reaction or an infusion-related reaction of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr • If an infusion-related reaction of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	Day 15	1,000 mg	
Cycles 2-6 or 2-8	Day 1	1,000 mg	
Monotherapy	Every 2 months for up to 2 years	1,000 mg	

Premedication & administration[1]

- Premedicate before each infusion
- Provide prophylactic hydration and antihyperuricemics to patients at high risk of tumor lysis syndrome
- Administer only as an intravenous infusion through a dedicated line
- Do not administer as an intravenous push or bolus
- Monitor blood counts at regular intervals
- GAZYVA 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

- If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible. During GAZYVA and chemotherapy treatment, adjust the dosing schedule accordingly to maintain the time interval between chemotherapy doses. During monotherapy, maintain the original dosing for subsequent doses. Initiate monotherapy approximately two months after the last dose of GAZYVA administered during the induction phase.

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Chemotherapy Regimen Dosing

Previously untreated FL[1]:

- **Bendamustine:** When combined with GAZYVA, bendamustine is administered at 90 mg/m^2 IV on Days 1 and 2 with prednisone 100 mg orally or equivalent on Day 1 of Cycle 1 for six 28-day cycles
- **CVP:** When combined with standard dosing of CVP, GAZYVA is administered over eight 21-day cycles
- **CHOP:** When combined with standard dosing of CHOP, GAZYVA is administered over six 21-day cycles followed by 2 additional cycles of GAZYVA alone, for a total of 8 GAZYVA cycles
- Patients who achieve a complete or partial response to the initial 6 or 8 cycles of GAZYVA treatment in combination with chemotherapy should continue on GAZYVA 1,000 mg as monotherapy every 2 months for up to 2 years

Relapsed or refractory FL:

- When combined with GAZYVA, bendamustine is administered at 90 mg/m^2 IV on Days 1 and 2 for six 28-day cycles
- Patients who achieve a complete response, partial response, or stable disease to the first 6 cycles of GAZYVA + bendamustine should continue on GAZYVA monotherapy every 2 months for up to 2 years

GAZYVA® obinutuzumab injection | 1,000mg/40mL

For Follicular Lymphoma

Recommended GAZYVA Infusion Rates[1]

Dilute GAZYVA with 0.9% sodium chloride to achieve a final concentration ranging from 0.4 mg/mL to 4 mg/mL.

- Do not use other diluents such as dextrose (5%)

Cycle 1, Day 1 (1,000 mg dose):

- Administer at 50 mg/hr. The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr

Cycle 1, Days 8 & 15; Cycles 2-6 or 2-8; Monotherapy (1,000 mg dose):

- If no infusion reaction or an infusion reaction of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
- If an infusion reaction of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr

For Follicular Lymphoma

Recommended GAZYVA Infusion Rates at Selected Concentrations[1]

If your desired mg/hr is:	At a 4 mg/mL concentration (1,000 mg in 250 mL), administer at:	At a 2 mg/mL concentration (1,000 mg in 500 mL), administer at:	At a 1 mg/mL concentration (1,000 mg in 1,000 mL), administer at:
50 mg/hr	13 mL/hr	25 mL/hr	50 mL/hr
100 mg/hr	25 mL/hr	50 mL/hr	100 mL/hr
150 mg/hr	38 mL/hr	75 mL/hr	150 mL/hr
200 mg/hr	50 mL/hr	100 mL/hr	200 mL/hr
250 mg/hr	63 mL/hr	125 mL/hr	250 mL/hr
300 mg/hr	75 mL/hr	150 mL/hr	300 mL/hr
350 mg/hr	88 mL/hr	175 mL/hr	350 mL/hr
400 mg/hr	100 mL/hr	200 mL/hr	400 mL/hr

This chart is provided as an example. Total volumes in IV bag could differ depending on overfill, withdrawal, and addition of fluid. Some numbers have been rounded.

When preparing a 1,000 mg dose for infusion, the PI recommends diluting 1,000 mg into a 250 mL 0.9% sodium chloride bag. GAZYVA can be administered at a final concentration of 0.4 mg/mL to 4 mg/mL.[1]

GAZYVA® obinutuzumab injection | 1,000mg/40mL

For Follicular Lymphoma

Recommended Premedications

The following premedications are recommended before GAZYVA infusion begins to reduce the risk of infusion-related reactions (IRRs)[1]

Complete before infusion	**Cycle 1:** Day 1	**All Subsequent Infusions**		
	All patients	**All patients**	**Patients with an IRR (Grade 1-2)** with the previous infusion	**Patients with a Grade 3 IRR** with the previous infusion OR with a lymphocyte count >25 x 10^9/L prior to next treatment
60 MINUTES **PRIOR** Intravenous glucocorticoid[a,b]	✓			✓
30 MINUTES **PRIOR** Antihistamine[c]	✓		✓	✓
30 MINUTES **PRIOR** Acetaminophen[d]	✓	✓	✓	✓

[a] 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion-related reactions.

[b] If a glucocorticoid-containing chemotherapy regimen is administered on the same day as GAZYVA, the glucocorticoid can be administered as an oral medication if given at least 1 hour prior to GAZYVA, in which case additional intravenous glucocorticoid as premedication is not required.

[c] Eg, 50 mg diphenhydramine.

[d] 650-1,000 mg.

Premedication and close monitoring are recommended for all patients[1]

- Patients with preexisting cardiac or pulmonary conditions are at a greater risk of experiencing more severe infusion-related reactions
- Hypotension may occur during GAZYVA intravenous infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration
- Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10^9/L) or renal impairment are considered at risk of tumor lysis syndrome and should receive prophylaxis. Premedicate with antihyperuricemics (eg, allopurinol or rasburicase) and ensure adequate hydration prior to start of GAZYVA therapy. Continue prophylaxis prior to each subsequent GAZYVA infusion, as needed
- Patients with Grade 3 to 4 neutropenia lasting more than one week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Consider antiviral and antifungal prophylaxis for patients with severe and long lasting (>1 week) neutropenia.

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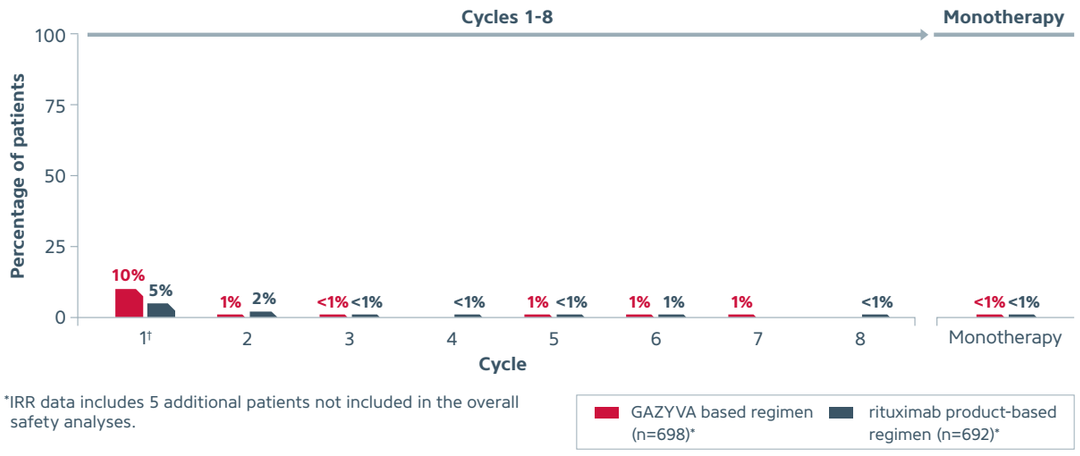
Incidence of IRRs in the GALLIUM Trial: Previously Untreated NHL

Infusion-related reactions (IRRs) with GAZYVA may be severe and life-threatening, and can occur at any time[1]

- Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, laryngeal edema)
- The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills

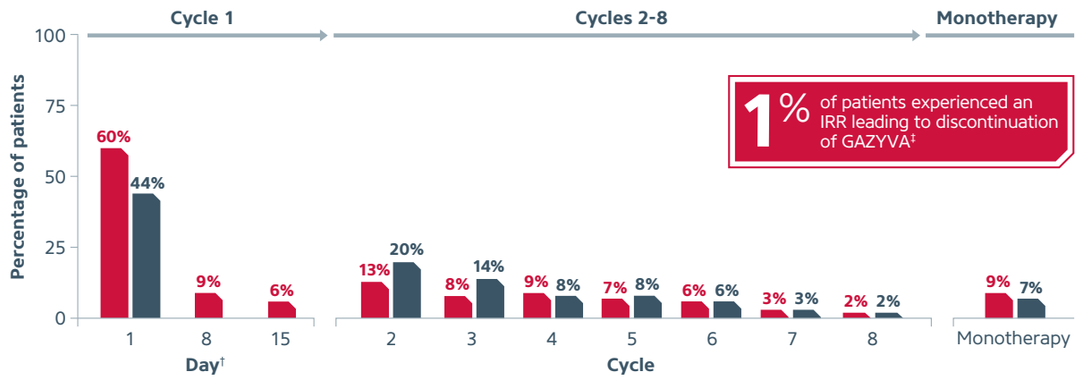
Grades 3 to 4 infusion-related reactions in the GAZYVA and rituximab product arms[2]



*IRR data includes 5 additional patients not included in the overall safety analyses.

GAZYVA based regimen (n=698)* | rituximab product-based regimen (n=692)*

Infusion-related reactions (all grades) in the GAZYVA and rituximab product arms[1,2]



†Per study protocol, GAZYVA was administered on Days 1, 8 and 15 of Cycle 1 and rituximab product was administered on Day 1 of Cycle 1.

‡In the rituximab product arm, <1% of patients experienced an IRR leading to treatment discontinuation.

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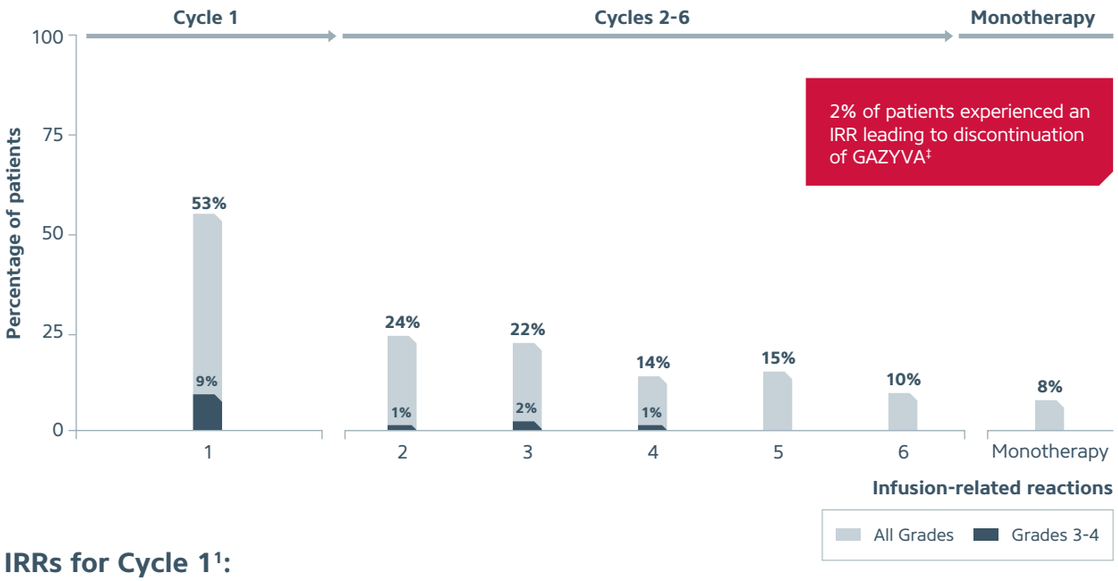
Incidence of IRRs in the GADOLIN Trial: Relapsed or Refractory NHL

Incidence of IRRs by treatment cycle in relapsed or refractory NHL[1,2]

- Patients relapsed or were refractory to a rituximab product-containing regimen

Incidence of IRRs in NHL patients treated with GAZYVA + bendamustine followed by GAZYVA monotherapy (n=194)[1,2]



IRRs for Cycle 1[1]:

- Grade 3-4 IRRs: 9%, All Grade IRRs: 53%
- The incidence of infusion-related reactions was highest on Day 1 (37%), and gradually decreased on Days 2,* 8, and 15 (23%, 6%, and 4%, respectively)

IRRs for subsequent cycles[1,2]

- Grade 3-4 IRRs: 1% in Cycle 2, 2% in Cycle 3, 1% in Cycle 4; absent in Cycles 5-6 and GAZYVA monotherapy
- All Grade IRRs: 24% in Cycle 2, 22% in Cycle 3, 14% in Cycle 4, 15% in Cycle 5, 10% in Cycle 6, and 8% in GAZYVA monotherapy

Overall IRR incidence rates during treatment with GAZYVA + bendamustine followed by GAZYVA monotherapy[1]

- Grade 3-4 IRRs: 11%
- All Grade IRRs: 67%

*Day 2 consisted of bendamustine only.

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For Follicular Lymphoma

Adjusting Infusions in Case of IRRs[1]

If a patient experiences an infusion-related reaction of any grade during infusion, adjust the infusion as follows:

Infusion-Related Reactions	CTCAE v5.0 Description[3]	Recommendations per Prescribing Information[1]
Grade 4 (life-threatening)	Life-threatening consequences; urgent intervention indicated	Stop infusion immediately and permanently discontinue GAZYVA therapy
Grade 3 (severe)	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Interrupt infusion and manage symptoms • Upon resolution of symptoms, consider restarting GAZYVA infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if patient does not experience any further IRRs, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose • Permanently discontinue treatment if patients experience a Grade 3 IRR symptom at rechallenge
Grades 1-2 (mild to moderate)	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Reduce infusion rate or interrupt infusion and manage symptoms • Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further IRRs, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose
	Mild transient reaction; infusion interruption not indicated; intervention not indicated	

- Closely monitor patients during the entire infusion. IRRs within 24 hours of receiving GAZYVA have occurred
- Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs

GAZYVA® obinutuzumab injection | 1,000mg/40mL

GAZYVA in Combination with Chlorambucil for the First-line Treatment of Chronic Lymphocytic Leukemia

Indication

GAZYVA, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation**
- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

Click here for full prescribing information and please see additional important safety information throughout, including BOXED WARNINGS.

Preparing to Administer GAZYVA

Prepare the solution for infusion, using aseptic technique, as follows[1]:

1. Inspect visually for any particulate matter and discoloration prior to administration

2. Dilute into a 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag. Do not use other diluents such as dextrose (5%)

3. Preparation of solution for infusion on:

- Day 1 (100 mg) and Day 2 (900 mg) of Cycle 1:
  - Prepare day 1 (100 mg) and day 2 (900 mg) infusion bags at the same time using one vial (1,000 mg/40 mL) on day 1
  - Withdraw 40 mL of GAZYVA solution from the vial
  - Dilute 4 mL (100 mg) of GAZYVA into a 100 mL 0.9% sodium chloride infusion bag for immediate administration
  - Dilute the remaining 36 mL (900 mg) into a 250 mL 0.9% sodium chloride infusion bag at the same time for use on Day 2 and store at 2°C to 8°C (36°F to 46°F) for up to 24 hours. After allowing the diluted bag to come to room temperature, use immediately
  - Clearly label each infusion bag
- Days 8 and 15 of Cycle 1 and Day 1 of Cycles 2-6:
  - Withdraw 40 mL of GAZYVA solution from the vial
  - Dilute 40 mL (1,000 mg) into a 250 mL 0.9% Sodium Chloride Injection, USP infusion bag

4. Mix diluted solution by gentle inversion. Do not shake or freeze

5. For microbiological stability, the diluted GAZYVA infusion solution should be used immediately. Dilute under appropriate aseptic conditions. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use

The product can be administered at a final concentration of 0.4 mg/mL to 4 mg/mL.

Dosage forms and strengths[1]

- 1,000 mg/40 mL (25 mg/mL) single-dose vial

For information on how to properly store GAZYVA, please refer to the enclosed full Prescribing Information.

GAZYVA® obinutuzumab injection | 1,000mg/40mL

Previously Untreated Chronic Lymphocytic Leukemia

6-Cycle Dosing Schedule

Each dose of GAZYVA is 1,000 mg administered intravenously with the exception of the first infusions in Cycle 1, which are administered on Day 1 (100 mg) and Day 2 (900 mg)[1]

GAZYVA dosing schedule[1]			
Day of treatment cycle		**Dose**	**Rate of infusion**
Cycle 1 (loading doses)	Day 1	100 mg	**Rate of infusion:** • Administer at 25 mg/hr over 4 hours • Do not increase the infusion rate
	Day 2	900 mg	**Rate of infusion:** • Administer at 50 mg/hr • The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
	Day 8	1,000 mg	**Rate of infusion:** • If no infusion-related reaction or an IRR of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr • If an IRR of Grade 2 or higher occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	Day 15	1,000 mg	
Cycles 2-6	Day 1	1,000 mg	

Chlorambucil should be given 0.5 mg/kg orally on Days 1 and 15 of Cycles 1-6

- If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible and adjust dosing schedule accordingly
- If appropriate, patients who do not complete the Day 1 Cycle 1 dose may proceed to the Day 2 Cycle 1 dose
- Consider treatment interruption if patients experience an infection, Grade 3 or 4 cytopenia, or a ≥Grade 2 non-hematologic toxicity

Premedication & administration[1]

- Premedicate before each infusion
- Provide prophylactic hydration and antihyperuricemics to patients at high risk of tumor lysis syndrome
- Administer only as an intravenous infusion through a dedicated line
- Do not administer as an intravenous push or bolus
- Monitor blood counts at regular intervals
- GAZYVA 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

Click here for full prescribing information and please see additional important safety information throughout, including BOXED WARNINGS.

Previously Untreated Chronic Lymphocytic Leukemia

Recommended Premedications

The following premedications are recommended before GAZYVA infusion begins to reduce the risk of infusion-related reactions (IRRs)[1]

Complete before infusion	**Cycle 1:** Days 1 and 2	**All Subsequent Infusions**		
	All patients	**All patients**	**Patients with an IRR (Grade 1-2)** with the previous infusion	**Patients with a Grade 3 IRR** with the previous infusion OR with a lymphocyte count >25 x 10^9/L prior to next treatment
60 MINUTES **PRIOR** Intravenous glucocorticoid[a,b]	✓			✓
30 MINUTES **PRIOR** Antihistamine[c]	✓		✓	✓
30 MINUTES **PRIOR** Acetaminophen[d]	✓	✓	✓	✓

[a] 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion-related reactions.

[b] If a glucocorticoid-containing chemotherapy regimen is administered on the same day as GAZYVA, the glucocorticoid can be administered as an oral medication if given at least 1 hour prior to GAZYVA, in which case additional intravenous glucocorticoid as premedication is not required.

[c] Eg, 50 mg diphenhydramine.

[d] 650-1,000 mg.

Premedication and close monitoring are recommended for all patients[1]

- Patients with preexisting cardiac or pulmonary conditions are at a greater risk of experiencing more severe infusion-related reactions
- Hypotension may occur as part of the GAZYVA infusion-related reaction. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each GAZYVA infusion and for the first hour after administration until blood pressure is stable
- Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10^9/L) or renal impairment are considered at risk of tumor lysis syndrome and should receive prophylaxis. Premedicate with antihyperuricemics (eg, allopurinol or rasburicase) and ensure adequate hydration prior to start of GAZYVA therapy. Continue prophylaxis prior to each subsequent GAZYVA infusion, as needed
- Patients with Grade 3 to 4 neutropenia lasting more than one week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Consider antiviral and antifungal prophylaxis for patients with severe and long lasting (>1 week) neutropenia.

GAZYVA® obinutuzumab injection | 1,000mg/40mL

Previously Untreated Chronic Lymphocytic Leukemia

Recommended GAZYVA Infusion Rates[1]

Dilute GAZYVA with 0.9% sodium chloride to achieve a final concentration ranging from 0.4 mg/mL to 4 mg/mL.

- Do not use other diluents such as dextrose (5%)

Cycle 1, Day 1 (100 mg dose):

- Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate
- The Day 1 dose for GAZYVA is 100 mg in 100 mL

Cycle 1, Day 2 (900 mg dose):

- If no infusion reaction occurred during the previous infusion, administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
- If an infusion reaction occurred during the previous infusion, administer at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr

Cycle 1, Days 8 &15; Cycles 2-6 (1,000 mg dose):

- If no infusion reaction occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
- If an infusion reaction occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr

Click here for full prescribing information and please see additional important safety information throughout, including BOXED WARNINGS.

Previously Untreated Chronic Lymphocytic Leukemia

Recommended GAZYVA Infusion Rates at Selected Concentrations[1]

If your desired mg/hr is:	At a 4 mg/mL concentration (1,000 mg in 250 mL), administer at:	At a 2 mg/mL concentration (1,000 mg in 500 mL), administer at:	At a 1 mg/mL concentration (1,000 mg in 1,000 mL), administer at:
25 mg/hr*	N/A	N/A	25 mL/hr
50 mg/hr	13 mL/hr	25 mL/hr	50 mL/hr
100 mg/hr	25 mL/hr	50 mL/hr	100 mL/hr
150 mg/hr	38 mL/hr	75 mL/hr	150 mL/hr
200 mg/hr	50 mL/hr	100 mL/hr	200 mL/hr
250 mg/hr	63 mL/hr	125 mL/hr	250 mL/hr
300 mg/hr	75 mL/hr	150 mL/hr	300 mL/hr
350 mg/hr	88 mL/hr	175 mL/hr	350 mL/hr
400 mg/hr	100 mL/hr	200 mL/hr	400 mL/hr

*The Day 1 dose for GAZYVA is 100 mg in 100 mL.

This chart is provided as an example. Total volumes in IV bag could differ depending on overfill, withdrawal, and addition of fluid. Some numbers have been rounded.

When preparing a 1,000 mg dose for infusion, the PI recommends diluting 1,000 mg into a 250 mL 0.9% sodium chloride bag. GAZYVA can be administered at a final concentration of 0.4 mg/mL to 4 mg/mL.[1]

GAZYVA® obinutuzumab injection | 1,000mg/40mL

Incidence of IRRs

IRRs with GAZYVA may be severe and life-threatening and can occur at any time[1]

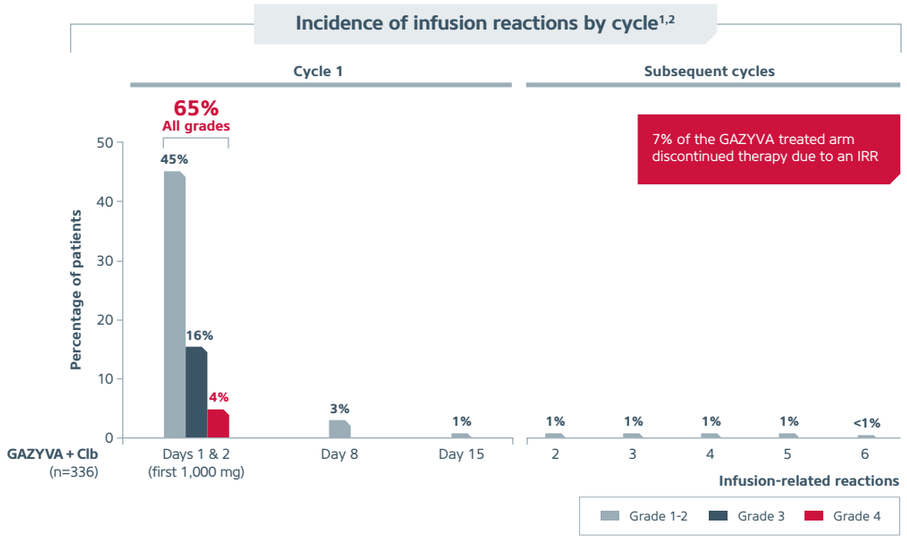
- Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (eg, bronchospasm, larynx and throat irritation, wheezing, laryngeal edema)
- The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills

First 1,000 mg infused: 65% of patients experienced IRRs with GAZYVA[1]

- Grade 3 or 4 reactions occurred in 20% of patients

Subsequent infusions: IRRs also occurred[1]

- The incidence of IRRs with subsequent infusions was 3% with the second 1,000 mg and <1% thereafter
- There were no Grade 3 or 4 IRRs reported after the first 1,000 mg infused



- In the rituximab product + Clb arm (n=321), the incidence of IRRs during Cycle 1 was 27% (24% Grades 1-2, 3% Grades 3-4)[2]
  - In Cycle 2, the incidence of IRRs was 13% (12% Grades 1-2, 1% Grades 3-4)
  - The incidence of IRRs was 6% for Cycle 3, 2% for Cycle 4, 2% for Cycle 5, and 1% for Cycle 6
  - <1% of the rituximab product treated arm discontinued therapy due to an IRR

Protocol modifications were implemented to help mitigate infusion-related reactions[1]

- Protocol modifications in CLL-11 required premedication with a corticosteroid,* an antihistamine, and acetaminophen. The first 1,000 mg dose was also divided into 2 infusions (100 mg on Day 1 and 900 mg on Day 2)

Before Protocol Modifications (n=53)

- **89%** of patients experienced an infusion-related reaction

After Protocol Modifications (n=140)

- **53%** of patients experienced an infusion-related reaction with the first 1,000 mg and <3% thereafter

*Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions.

Adjusting Infusions in Case of IRRs[1]

If a patient experiences an infusion-related reaction of any grade during infusion, adjust the infusion as follows:

Infusion-Related Reactions	CTCAE v5.0 Description[3]	Recommendations per Prescribing Information[1]
Grade 4 (life-threatening)	Life-threatening consequences; urgent intervention indicated	Stop infusion immediately and permanently discontinue GAZYVA therapy
Grade 3 (severe)	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Interrupt infusion and manage symptoms • Upon resolution of symptoms, consider restarting GAZYVA infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose • Permanently discontinue treatment if patients experience a Grade 3 IRR symptom at rechallenge
Grades 1-2 (mild to moderate)	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Reduce infusion rate or interrupt infusion and manage symptoms • Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further IRRs, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose
	Mild transient reaction; infusion interruption not indicated; intervention not indicated	

CTCAE, Common Terminology Criteria for Adverse Events.

- Closely monitor patients during the entire infusion. IRRs within 24 hours of receiving GAZYVA have occurred
- Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs

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GAZYVA® obinutuzumab injection | 1,000mg/40mL

Important Safety Information

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation**
- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

Contraindications

- GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g. anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use

Warnings and Precautions

Hepatitis B Virus Reactivation

- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies including GAZYVA. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (ie, 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 level, 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, ie, increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death
- Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with GAZYVA. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult healthcare providers with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy
- 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 treatment with GAZYVA
- In patients who develop reactivation of HBV while receiving GAZYVA, immediately discontinue GAZYVA and any concomitant chemotherapy and institute appropriate treatment. Resumption of GAZYVA in patients whose HBV reactivation resolves should be discussed with healthcare providers with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming GAZYVA in patients who develop HBV reactivation

Progressive Multifocal Leukoencephalopathy (PML)

- JC virus infection resulting in PML, which can be fatal, occurred in patients treated with GAZYVA. Consider the diagnosis of PML in any patient presenting with new onset or changes to preexisting neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue GAZYVA therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML

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Important Safety Information (cont'd)

Infusion-Related reactions

- GAZYVA can cause severe and life-threatening infusion-related reactions (IRRs). Sixty-five percent of patients with CLL experienced a reaction to the first 1,000 mg of GAZYVA infused. Thirty-seven percent of patients with relapsed or refractory NHL and 60% of patients with previously untreated NHL experienced a reaction on Day 1 of GAZYVA infusion. IRRs have occurred within 24 hours of receiving GAZYVA. IRRs can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, and laryngeal edema). The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills
- Premedicate patients with acetaminophen, an antihistamine, and a glucocorticoid. Closely monitor patients during the entire infusion. Reduce infusion rate, interrupt infusion or permanently discontinue GAZYVA for IRRs based on severity. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed
- For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period since they may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the GAZYVA infusion-related reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each GAZYVA infusion, and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication

Hypersensitivity Reactions Including Serum Sickness

- Hypersensitivity reactions have been reported in patients treated with GAZYVA. Signs of immediate-onset hypersensitivity included dyspnea, bronchospasm, hypotension, urticaria and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported with symptoms that include chest pain, diffuse arthralgia and fever. Hypersensitivity reactions may be difficult to clinically distinguish from infusion-related reactions. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure.
- If a hypersensitivity reaction is suspected during or after an infusion, stop the infusion and permanently discontinue treatment. GAZYVA is contraindicated in patients with known hypersensitivity reactions to GAZYVA, including serum sickness with prior obinutuzumab use

Tumor Lysis Syndrome (TLS)

- Tumor lysis syndrome, including fatal cases, has been reported in patients receiving GAZYVA. Patients with high tumor burden, high circulating lymphocyte count (>25 x 10^9/L) or renal impairment are at greater risk for TLS
- Administer appropriate tumor lysis prophylaxis with antihyperuricemics (eg, allopurinol or rasburicase) and hydration prior to the infusion of GAZYVA for patients at risk for TLS. During the initial days of GAZYVA treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated

Infections

- Fatal and serious bacterial, fungal, and new or reactivated viral infections can occur during and following GAZYVA therapy. When GAZYVA is administered with chemotherapy followed by GAZYVA monotherapy, Grade 3 to 5 infections have been reported in up to 8% of patients during combination therapy, up to 13% of patients during monotherapy, and up to 8% of patients after treatment

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Important Safety Information (cont'd)

Infections (cont'd)

- In GALLIUM, more Grade 3 to 5 infections were reported in the recipients of GAZYVA and bendamustine (117/410 patients, 29%), as compared to GAZYVA plus CHOP or CVP (43/281 patients, 15%). More fatal infections were reported in patients treated with GAZYVA and bendamustine (3%), as compared to GAZYVA plus CHOP or CVP (<1%), including during the monotherapy phase and after completion of treatment
- Do not administer GAZYVA to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection

Neutropenia

- Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with GAZYVA. Monitor patients with Grade 3 to 4 neutropenia frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Consider dose delays for Grade 3 or 4 neutropenia
- Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days)
- Patients with severe and long lasting (>1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Consider antiviral and antifungal prophylaxis

Thrombocytopenia

- Severe and life-threatening thrombocytopenia has been reported during treatment with GAZYVA in combination with chemotherapy. Fatal hemorrhagic events have been reported in patients with NHL treated with GAZYVA in combination with chemotherapy, including during Cycle 1
- Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider dose delays of GAZYVA and chemotherapy or dose reductions of chemotherapy. Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications that may increase bleeding risk (platelet inhibitors or anticoagulants), especially during the first cycle

Immunization

- The safety and efficacy of immunization with live or attenuated viral vaccines during or following GAZYVA therapy have not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery

Embryo-Fetal Toxicity

- Based on its mechanism of action and findings in animals, GAZYVA can cause B-cell depletion in infants exposed to obinutuzumab in-utero. Advise pregnant women of the potential risk to a fetus. Mothers who have been exposed to GAZYVA during pregnancy should discuss the safety and timing of live virus vaccinations for their infants with their child's healthcare providers. Advise females of reproductive potential to use effective contraception while receiving GAZYVA and for 6 months after the last dose

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Important Safety Information (cont'd)

Lactation

- Human IgG is known to be present in human milk. Because of the potential of serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with GAZYVA and for 6 months after the last dose

Geriatric Use

- Of 336 patients with previously untreated CLL who received GAZYVA in combination with chlorambucil, 81% were 65 years and older, while 46% were 75 and older. Of the patients 75 years and older, 46% experienced serious adverse reactions and 7% experienced adverse reactions leading to death. Of the patients younger than 75, 33% experienced a serious adverse reaction and 2% an adverse reaction leading to death. No significant differences in efficacy were observed between younger and older patients
- Of 204 patients in GADOLIN with relapsed or refractory NHL treated with GAZYVA plus bendamustine, 44% were 65 and over, while 14% were 75 and over. In patients 65 and over, 55% of patients experienced serious adverse reactions and 28% experienced adverse reactions leading to treatment withdrawal while in patients under 65, 37% and 14% experienced serious adverse reactions and adverse reactions leading to treatment withdrawal, respectively. No clinically meaningful differences in efficacy were observed between these patients and younger patients in GADOLIN
- Of the 691 patients in GALLIUM treated with GAZYVA plus chemotherapy as first-line therapy, 33% were 65 and over, while 7% were 75 and over. Of patients 65 and over, 63% experienced serious adverse reactions and 26% experienced adverse reactions leading to treatment withdrawal, while in patients under 65, 43% experienced serious adverse reactions and 13% had an adverse reaction leading to treatment withdrawal. No clinically meaningful differences in efficacy were observed between these patients and younger patients

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Important Safety Information (cont'd)

Additional Important Safety Information

Previously Untreated CLL

- The most common Grade 3 to 4 adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVA containing arm were neutropenia, infusion-related reactions, and thrombocytopenia
- The most common adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVA containing arm were infusion-related reactions, neutropenia, thrombocytopenia, and diarrhea
- Adverse reactions rates and laboratory abnormalities from the Stage 2 phase are consistent with the rates in Stage 1. In addition to the adverse reactions observed in Stage 2, in Stage 1 back pain (5% vs 2%), anemia (12% vs 10%) and cough (10% vs 7%) were observed at a higher incidence in the GAZYVA treated patients. The incidence of Grade 3 to 4 back pain (<1% vs 0%), cough (0% vs <1%) and anemia (5% vs 4%) was similar in both treatment arms. With regard to laboratory abnormalities, in Stage 1 hyperkalemia (33% vs 18%), creatinine increased (30% vs 20%) and alkaline phosphatase increased (18% vs 11%) were observed at a higher incidence in patients treated with GAZYVA with similar incidences of Grade 3 to 4 abnormalities between the two arms

Relapsed/Refractory NHL

- The GADOLIN study evaluated safety in 407 patients with relapsed or refractory NHL, including FL (81%), small lymphocytic lymphoma (SLL) and marginal zone lymphoma (MZL) (a disease for which GAZYVA is not indicated), who did not respond to or progressed within 6 months of treatment with rituximab product or a rituximab product-containing regimen. In patients with follicular lymphoma, the profile of adverse reactions was consistent with the overall NHL population
- Serious adverse reactions occurred in 45% of the GAZYVA arm and 37% of the bendamustine-only arm. Fatal adverse reactions within 90 days of treatment occurred in 3.4% and 2.5%, respectively. Throughout follow-up, fatal adverse reactions occurred in 10% of GAZYVA recipients and in 7.4% of recipients of bendamustine alone, with infection and second primary malignancies being the leading causes
- The most common adverse reactions (incidence ≥20%) in GAZYVA recipients included infusion-related reactions, fatigue, neutropenia, cough, upper respiratory tract infections, and musculoskeletal pain
- During GAZYVA monotherapy (158 patients), adverse reactions in ≥10% of patients included upper and lower respiratory tract infections, cough, neutropenia, musculoskeletal pain, fatigue, diarrhea, rash, and urinary tract infection
- In the GAZYVA monotherapy phase, new or worsening Grade 3 or 4 abnormalities included neutropenia in 25% of patients (Grade 4, 10%) and lymphopenia in 23% (Grade 4, 5%)

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Previously Untreated NHL

- A randomized, open-label multicenter trial (GALLIUM) evaluated the safety of GAZYVA as compared to rituximab product in 1,385 patients with previously untreated follicular lymphoma (86%) or marginal zone lymphoma (14%)
- Serious adverse reactions occurred in 50% of patients on the GAZYVA arm and 43% of patients on the rituximab product arm. Fatal adverse reactions were reported during treatment in 3% in the GAZYVA arm and 2% in the rituximab product arm, most often from infections in the GAZYVA arm. During treatment and follow-up combined, fatal adverse reactions were reported in 5% of the GAZYVA arm and 4% of the rituximab product arm, with infections and second malignancies being leading causes. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to <1% in the rituximab product arm
- Neutropenia, infusion related reactions, febrile neutropenia and thrombocytopenia were the most common Grade 3 to 5 adverse reactions (incidence ≥5%) observed more frequently in the GAZYVA arm
- Throughout treatment and follow-up, the most common adverse reactions (incidence ≥20%) observed at least 2% more in the GAZYVA arm were infusion related reactions (72%), neutropenia (53%), upper respiratory tract infection (50%), cough (35%), constipation (32%) and diarrhea (30%)
- During the monotherapy period, the common adverse reactions (incidence ≥10%) observed at least 2% more with GAZYVA were upper respiratory infection (40%), cough (23%), musculoskeletal pain (20%), neutropenia (19%) and herpesvirus infection (13%)

You are encouraged to report side effects to Genentech and the FDA. You may contact Genentech by calling 1-888-835-2555. You may contact the FDA by visiting www.fda.gov/medwatch, or calling 1-800-FDA-1088.

References: 1. GAZYVA full Prescribing Information. South San Francisco, CA: Genentech, Inc.; 2020. **2.** Data on file. Genentech, Inc. **3.** Common terminology criteria for adverse events (CTCAE). National Cancer Institute Website. Updated November 27, 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed June 17, 2019.

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