GAZYVA for Chronic Lymphocytic Leukemia (CLL)

GAZYVA is a prescription medicine used with the chemotherapy drug, chlorambucil, to treat chronic lymphocytic leukemia (CLL) in adults who have not had previous CLL treatment.

WHAT IS THE MOST IMPORTANT SAFETY INFORMATION I SHOULD KNOW ABOUT GAZYVA?

Tell your doctor right away about any side effect you experience. GAZYVA can cause side effects that can become serious or life threatening, including:

- **Hepatitis B Virus (HBV):** Hepatitis B can cause liver failure and death. If you have a history of hepatitis B infection, GAZYVA could cause it to return. You should not receive GAZYVA if you have active hepatitis B liver disease. Your doctor or healthcare team will need to screen you for hepatitis B before, and monitor you during and after, your treatment with GAZYVA. Sometimes this will require treatment for hepatitis B. Symptoms of hepatitis include: worsening of fatigue and yellow discoloration of skin or eyes.

- **Progressive Multifocal Leukoencephalopathy (PML):** PML is a rare and serious brain infection caused by a virus. PML can be fatal. Your weakened immune system could put you at risk. Your doctor will watch for symptoms. Symptoms of PML include: confusion, difficulty talking or walking, dizziness or loss of balance, and vision problems.

Please see pages 18-23 and accompanying full Prescribing Information for additional Important Safety Information, including BOXED WARNINGS.
Your doctor says it is time to treat your chronic lymphocytic leukemia (CLL) with GAZYVA® (obinutuzumab).

You may have a few questions. This guide will help explain CLL and your course of treatment with GAZYVA.

Please contact your healthcare treatment team with any questions that you may have.

Who should not receive GAZYVA?

- Do NOT receive GAZYVA if you have had an allergic reaction (eg, anaphylaxis or serum sickness) to GAZYVA. Tell your healthcare provider if you have had an allergic reaction to obinutuzumab or any other ingredients in GAZYVA in the past.

The information provided in this brochure is meant for informational purposes only. It is not meant to replace your physician’s medical advice.
In this guide:

About CLL
Treatment goals and options
About GAZYVA® (obinutuzumab)
What to expect with GAZYVA treatment
GAZYVA safety information
Most common side effects
Glossary
Support and resources
Talking with your doctor
Contacts
Notes

Certain medical terms used in this guide in **bold** and *underlined* will be defined in the Glossary.
What is CLL?

CLL stands for **chronic lymphocytic leukemia**. It is a type of blood cancer that involves **lymphocytes**—white blood cells that help fight infections. When you have CLL, abnormal lymphocytes build up in the blood and **bone marrow**. Over time, these abnormal cells crowd the healthy cells. The result is fewer healthy white blood cells, red blood cells, and **platelets**. This leads to problems such as infection, **anemia**, and excess bruising and bleeding. Abnormal lymphocytes may also build up in **lymph nodes**, the liver, or the **spleen** (an organ in your abdomen). This can lead to swelling of these organs.
What are the symptoms of CLL?

Everyone experiences CLL differently. CLL does not always cause symptoms. In early stages of CLL, you are less likely to be bothered by symptoms. Still, it is important to pay attention to how your CLL may be affecting you. Tell your doctor if you notice any symptoms or changes in your health.

The symptoms you should watch for include:

- Weakness
- Feeling tired
- Feeling short of breath
- Weight loss
- Fever
- Night sweats

Symptoms of CLL may be seen in other conditions as well. Only your doctor will be able to tell if your symptoms are related to CLL.

Your doctor will be looking for:

- An increase in the number of abnormal white blood cells
- A decrease in the number of normal blood cells
- Swelling in your lymph nodes, liver, or spleen

Worsening of symptoms is reason to start treatment for CLL. Remember to talk with your healthcare team.
Understanding medical tests for CLL

CLL cannot be diagnosed by symptoms alone. In fact, you are often not the first to notice your CLL. CLL is usually detected by routine checkups, or blood work for other health issues. Your doctor will need to use medical tests to diagnose your CLL. Medical tests will also tell where CLL is in your body.

**Common tests for diagnosis or prior treatment:**
- **Physical exam**—your doctor checks for swollen lymph nodes, liver, or spleen and other signs of CLL
- **Blood cell counts**—your blood is taken through a vein and examined in a lab. Most people with CLL have a high white blood cell count
- **Biopsy**—a small sample of bone marrow or lymph node is removed and viewed under a microscope
- **Flow cytometry**—a sample of your cells is examined using a laser beam and a computer to find out the type of cancer and the number of cells involved

**Common tests to find out where CLL is in your body include:**
- **Imaging tests such as CT scans**—these are pictures of the inside of your body that help show where CLL is
How do I know how advanced my CLL is?

Your doctor may talk about your CLL as being a certain stage. Stages are a way for your healthcare team to talk about how advanced your cancer is. Your stage is based on how many CLL cells you have and where they are in your body. This translates into early, intermediate, or advanced CLL.

Staging and the presence of symptoms often help your medical team determine:

1) if treatment is necessary at this time, and
2) what the most appropriate treatment is
# 5 stages of chronic lymphocytic leukemia

<table>
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<tr>
<th>Stages</th>
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<td>Early</td>
<td>0  - High lymphocyte count in the blood</td>
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<td>Intermediate</td>
<td>I  - High lymphocyte count in the blood</td>
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<td>- Swollen lymph nodes</td>
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<td>II - High lymphocyte count in the blood</td>
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<td>- Swollen spleen or liver</td>
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<td>- With or without swollen lymph nodes</td>
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<tr>
<td>Advanced</td>
<td>III - High lymphocyte count in the blood</td>
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<td>- Low red blood cell count (anemia)</td>
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<td>- With or without swollen lymph nodes, spleen, or liver</td>
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<td>IV  - High lymphocyte count in the blood</td>
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<td></td>
<td>- Too few blood platelets</td>
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<td></td>
<td>- With or without anemia or swollen lymph nodes, spleen, or liver</td>
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For definitions of certain medical terms, please see the Glossary on pages 24 and 25.
What are the goals of treatment?

There is no cure for CLL. As a result, the goals of treatment are to relieve symptoms, stop the cancer from getting worse, or achieve remission.

Treatment goals and options depend on how much your symptoms are affecting you:

- **When you don’t have symptoms**, close monitoring is usually preferred over treatment. This is often referred to as “watch and wait”
- **When symptoms appear or worsen**, treatment aims to stop the CLL from progressing

If your doctor says you need treatment, there are many options to help manage your CLL. CLL can be treated in a number of ways, including antibody therapy and/or chemotherapy. Often, doctors will combine the two types of treatment for better results.

**Once you begin treatment, your doctor will need to regularly check your**:

- Symptoms
- Size of lymph nodes, liver, or spleen
- Blood count measures
**Antibody therapy**

**Antibody therapy** is used to find and destroy specific cells within the body. It can use your body’s immune system to help fight cancer. It can also harm healthy cells in the body. It is often an important part of CLL treatment plans and can be given along with chemotherapy.

**How it works**
Antibody therapy targets a protein found on the surface of both CLL cells and some healthy blood cells. It is thought to use your body’s immune system to find and kill leukemia and healthy cells.

**Chemotherapy**

**Chemotherapy** is a drug treatment that destroys growing cells, including cancer cells. It is also an important part of CLL treatment plans. It can be given as a single drug or a combination of drugs including antibody therapy.

**How it works**
Chemotherapy attacks growing cancer cells in the body. It also attacks growing healthy cells in the body, such as those for hair and the intestinal lining.
What is GAZYVA?

GAZYVA® (obinutuzumab) is a type of antibody therapy that targets and attaches to the CD20 proteins found on CLL cells and some healthy blood cells.

Once attached to the CD20 protein, GAZYVA is thought to work in different ways, including:
• By helping your own immune system destroy the cancer cells
• By destroying the cancer cells directly

In addition, GAZYVA can harm healthy cells in your body.

Starting treatment with GAZYVA

On the days you receive GAZYVA, you should expect to spend most of the day at the clinic or infusion center. Your doctor may have you take medications one hour before you begin taking GAZYVA. Your doctor may refer to this kind of medication as premedication.

Common premedications include acetaminophen, antihistamines, and steroid medications. Taking the suggested medication before treatment may reduce the chance of possible side effects during your GAZYVA infusion. Be sure to check with your medical team about the proper premedication you should take before taking GAZYVA.
Please see pages 18-23 and accompanying full Prescribing Information for Important Safety Information, including BOXED WARNINGS.
How and when am I given GAZYVA?

GAZYVA® (obinutuzumab) is given as an infusion. This means it goes directly into your vein through a needle in your arm. You’ll get your treatment with GAZYVA at the clinic or infusion center.

GAZYVA is given for a total of 6 cycles, or rounds, of treatment. Each cycle will last 28 days. Treatment occurs only on certain days of each cycle, and that is usually followed by several weeks of rest and recovery. **This means that most people will complete their GAZYVA treatment in about 6 months.**

Each dose of GAZYVA is the same except for the first two days of Cycle 1. This is done to help reduce side effects you may have during the infusion. Some patients may have side effects during the infusion process. Please refer to page 17 for more information about these reactions.

_Speak with your doctor if you miss a dose of GAZYVA._

GAZYVA® (obinutuzumab) is a prescription medicine used with the chemotherapy drug, chlorambucil, to treat chronic lymphocytic leukemia (CLL) in adults who have not had previous CLL treatment.
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Preparing for your infusion

One week before:
- Tell your doctor about all the medicines you take, including prescription and non-prescription medicine, vitamins, and herbal supplements
- Speak to your doctor if you take medications to control your blood pressure. He/she may ask you to not take them on the day of your GAZYVA® (obinutuzumab) infusion
- Arrange a ride—after your infusion, you may feel drowsy or dizzy. It is a good idea to have someone else drive you home

One day before:
- Remember to follow any changes your doctor made to your regular medication schedule

The day of your infusion
At home:
- Wear or bring loose clothing so you can be comfortable during your infusion
- Pack food and drink—bringing some snacks or a packed meal can help you get through the day
- Bring a book or activities to help pass the time

At the clinic or infusion center:
- Take the medications prescribed by your doctor to help reduce the side effects of the infusion process
- Relax during your infusion, but be aware of what is happening to your body. Tell your doctor or nurse right away if you feel any side effects, including the symptoms of an infusion reaction
Infusion Reactions

These side effects may occur during or within 24 hours of any GAZYVA® (obinutuzumab) infusion. Some infusion reactions can be serious, including, but not limited to, severe allergic reactions (anaphylaxis), acute life-threatening breathing problems, or other life-threatening infusion reactions. If you have a reaction, the infusion is either slowed or stopped until your symptoms are resolved. Most patients are able to complete infusions and receive medication again. However, if the infusion reaction is serious, the infusion of GAZYVA will be permanently stopped. Your healthcare team will take steps to help lessen any side effects you may have to the infusion process. You may be given medicines to take before each GAZYVA treatment.

Signs of infusion reactions may include:

- Tiredness
- Dizziness
- Headache
- Redness of the face
- Nausea
- Chills
- Fever
- Vomiting
- Diarrhea
- Breathing problems
- Chest pain
Important safety information about GAZYVA

What is the most important safety information I should know about GAZYVA® (obinutuzumab)?
Tell your doctor right away about any side effect you experience. GAZYVA can cause side effects that can become serious or life threatening, including:

Hepatitis B Virus (HBV)
Hepatitis B can cause liver failure and death. If you have a history of hepatitis B infection, GAZYVA could cause it to return. You should not receive GAZYVA if you have active hepatitis B liver disease. Your doctor or healthcare team will need to screen you for hepatitis B before, and monitor you during and after, your treatment with GAZYVA. Sometimes this will require treatment for hepatitis B. Symptoms of hepatitis include: worsening of fatigue and yellow discoloration of skin or eyes.

Progressive Multifocal Leukoencephalopathy (PML)
PML is a rare and serious brain infection caused by a virus. PML can be fatal. Your weakened immune system could put you at risk. Your doctor will watch for symptoms. Symptoms of PML include: confusion, difficulty talking or walking, dizziness or loss of balance, and vision problems.

Who should not receive GAZYVA?
Do NOT receive GAZYVA if you have had an allergic reaction (eg, anaphylaxis or serum sickness) to GAZYVA. Tell your healthcare provider if you have had an allergic reaction to obinutuzumab or any other ingredients in GAZYVA in the past.

Please see accompanying full Prescribing Information for additional Important Safety Information, including BOXED WARNINGS.
What are the additional possible serious side effects of GAZYVA® (obinutuzumab)?

Tell your doctor right away about any side effect you experience. GAZYVA can cause side effects that may become severe or life threatening, including:

**Infusion Reactions**

These side effects may occur during or within 24 hours of any GAZYVA infusion. Some infusion reactions can be serious, including, but not limited to, severe allergic reactions (anaphylaxis), acute life-threatening breathing problems, or other life-threatening infusion reactions. If you have a reaction, the infusion is either slowed or stopped until your symptoms are resolved. Most patients are able to complete infusions and receive medication again. However, if the infusion reaction is serious, the infusion of GAZYVA will be permanently stopped. Your healthcare team will take steps to help lessen any side effects you may have to the infusion process. You may be given medicines to take before each GAZYVA treatment. Symptoms of infusion reactions may include: fast heartbeat, tiredness, dizziness, headache, redness of the face, nausea, chills, fever, vomiting, diarrhea, rash, high blood pressure, low blood pressure, difficulty breathing, and chest discomfort.

**Hypersensitivity Reactions Including Serum Sickness**

Some people receiving GAZYVA may have severe or life-threatening allergic reactions. This reaction may be severe, may happen during or after an infusion, and may affect many areas of the body. If an allergic reaction occurs, your doctor will stop the infusion and permanently discontinue GAZYVA.
Important safety information about GAZYVA (cont’d)

Tumor Lysis Syndrome (TLS)
Tumor lysis syndrome, including fatal cases, has been reported in patients receiving GAZYVA® (obinutuzumab). GAZYVA works to break down cancer cells quickly. As cancer cells break apart, their contents are released into the blood. These contents may cause damage to organs and the heart, and may lead to kidney failure requiring the need for dialysis treatment. Your doctor may prescribe medication to help prevent TLS. Your doctor will also conduct regular blood tests to check for TLS. Symptoms of TLS may include nausea, vomiting, diarrhea, and tiredness.

Infections
While you’re taking GAZYVA, you may develop infections. Some of these infections may be fatal and severe, so be sure to talk to your doctor if you think you have an infection. Patients with a history of recurring or chronic infections may be at an increased risk of infection. Patients with an active infection should not be treated with GAZYVA.

Low White Blood Cell Count
When you have an abnormally low count of infection-fighting white blood cells, it is called neutropenia. While you are taking GAZYVA, your doctor will do blood work to check your white blood cell count. Severe and life-threatening neutropenia can develop during or after treatment with GAZYVA. Some cases of neutropenia can last for more than one month. If your white blood cell count is low, your doctor may prescribe medication to help prevent infections.
Low Platelet Count

Platelets help stop bleeding or blood loss. GAZYVA® (obinutuzumab) may reduce the number of platelets you have in your blood; having low platelet count is called thrombocytopenia. This may affect the clotting process. While you are taking GAZYVA, your doctor will do blood work to check your platelet count. Severe and life-threatening thrombocytopenia can develop during or after treatment with GAZYVA. If your platelet count gets too low, your treatment may be delayed or reduced.

The most common side effects of GAZYVA are infusion reactions, low white blood cell counts, low platelet counts, low red blood cell counts, fever, cough, nausea, and diarrhea.

What other information should I tell my doctor before receiving GAZYVA?

You should talk to your doctor about:

Immunizations

Before receiving GAZYVA therapy, tell your healthcare provider if you have recently received or are scheduled to receive a vaccine. People who are treated with GAZYVA should not receive live vaccines.

Pregnancy

Tell your doctor if you are pregnant, think that you might be pregnant, plan to become pregnant, or are breastfeeding. GAZYVA may harm your unborn baby. Speak to your doctor about using GAZYVA while you are pregnant. Talk to your doctor or your child’s doctor about the safety and timing of live virus vaccinations to your infant if you received GAZYVA during pregnancy. It is not known if GAZYVA may pass into your breast milk. Speak to your doctor about using GAZYVA if you are breastfeeding.
**Side effects in a clinical trial**

The following side effects have occurred with GAZYVA® (obinutuzumab) infusions:

**Infusion reactions**
- First 2 days of treatment – 65%
- Later infusions – 3%

**Low counts of certain cells within the blood**
- White blood cells – 38%
- Platelets – 14%
- Red blood cells – 11%

Fever – 10%
Cough – 10%
Nausea – 12%
Diarrhea – 10%
Tell your doctor about any side effects.

These are not all of the possible side effects of GAZYVA® (obinutuzumab). For more information, ask your doctor or pharmacist.

GAZYVA is available by prescription only.

You may report side effects to the FDA at (800) FDA-1088, or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see the accompanying full Prescribing Information, including BOXED WARNINGS, for additional Important Safety Information.

Remember to tell your healthcare team exactly how you feel. This will allow them to take the proper actions to help you.
**Glossary**

**Anemia**: Having too few red blood cells in the body. This can cause a person to feel tired, weak, and short of breath because the tissues are not getting enough oxygen.

**Antibody therapy**: A type of therapy used to find and destroy specific cells within the body (for example, the cells where CLL starts). Antibody therapy can also harm healthy cells in the body. This is a type of immunotherapy.

**Bone marrow**: The soft spongy material that fills the inside of bones. Bone marrow is the source of new blood cells, and platelets are made in the bone marrow.

**Chemotherapy**: A drug treatment that destroys fast-growing cells, including cancer cells.

**Chronic lymphocytic leukemia (CLL)**: One type of blood cancer or leukemia. With CLL, the blood or bone marrow has too many white blood cells, known as lymphocytes.

**CT (computed tomography) scan**: A medical test that uses a computer linked to an x-ray machine to take pictures of the inside of the body.

**Flow cytometry**: This test identifies the type of blood cancer and number of cells involved.

**Immune cells**: Cells that defend the body from infection. These cells are part of the immune system.

**Immune system**: The group of organs and cells that defend the body from infections.

**Immunotherapy**: A treatment (such as antibodies) that uses your body’s immune system to help fight cancer. Immunotherapy can also harm healthy cells in the body.

**Leukemia**: A cancer of white blood cells.

**Lymph node**: A small bean-shaped organ that stores white blood cells.
**Lymphocytes:** A type of white blood cell that has an important role in fighting infection.

**Platelet:** A type of cell found in the blood and spleen. Platelets help prevent bleeding by forming blood clots.

**Relapse:** A term used to describe the return of disease after it has responded to treatment.

**Remission:** A term used to describe a response to treatment. Partial remission means the cancer is significantly improved, but evidence of the cancer remains. Complete remission means all evidence of the cancer is gone for a period of time.

**Spleen:** An organ that is part of the lymphatic system. The spleen makes lymphocytes, filters blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach.

**Watch and wait:** A period of time when patients, along with their doctor, watch the disease and do not start treatment unless needed.
Support and resources

Support from Genentech

Genentech BioOncology® Co-pay Card Program
The Genentech BioOncology® Co-pay Card program helps people with commercial health insurance. This might be a plan you get through your employer or one you purchased through a Health Insurance Marketplace like HealthCare.gov. To qualify, you must also meet other criteria.

Independent Co-pay Assistance Foundations
If you need help with your co-pay for your Genentech medicine, GAZYVA Access Solutions can refer you to an independent co-pay assistance foundation. Independent co-pay assistance foundations help patients with public health insurance or commercial health insurance.

The Genentech® Access to Care Foundation (GATCF)
GATCF helps people who don’t have health insurance. It also helps people who have health insurance but have trouble paying for GAZYVA. If you qualify for GATCF, you could receive your medicine for free.

To learn more about how we can help,
CALL 1 866-422-2377
VISIT www.genentech-access.com/GAZYVA/patients
Helpful resources

Many patient support groups offer helpful information about cancer. Some may also help you connect with a local support group. You can share your experiences and learn more about CLL. Many people find this helps them stay informed and stay positive.

**Cancer organizations**

**American Cancer Society**
1-800-ACS-2345 (1-800-227-2345)
www.cancer.org

**CancerCare, Inc.**
1-800-813-HOPE (1-800-813-4673)
www.cancercare.org

**National Cancer Institute**
1-800-4-CANCER (1-800-422-6237)
www.cancer.gov

**National Comprehensive Cancer Network**
www.nccn.org/patients

**Leukemia organizations**

**Lymphoma Research Foundation**
1-800-500-9976
www.lymphoma.org

**The Leukemia & Lymphoma Society**
1-800-955-4572
www.lls.org

**Support organizations**

**Cancer Support Community**
1-888-793-WELL (1-888-793-9355)
www.cancersupportcommunity.org

**Patient Advocate Foundation**
1-800-532-5274
www.patientadvocate.org

Genentech is not affiliated with any of these organizations. The information provided by Genentech or these organizations is meant for informational purposes only. It is not meant to replace your physician’s medical advice.
Questions to ask your doctor

Before starting treatment, it is important to ask your doctor or nurse any questions you may have. It is a good idea to write down a list of questions before your appointment. Bring a family member or friend to your appointment for support. They can also help you keep track of the answers.

Here are some questions to consider asking:

• What are my treatment options?
• What will my treatment schedule be?
• Do I need to take medication at home as well?
• What are the possible side effects of treatment?
• Is there more I can do to make the most of my treatment?
• Where can I find information about support to help me pay for my GAZYVA® (obinutuzumab) therapy?
• Where can I get more information about CLL?
• How will treatment with GAZYVA affect my lifestyle (working, traveling, etc)?
Use this space to help keep track of important contact information.

**Doctor (Name):**

- Phone: 
- Email: 

**Nurse (Name):**

- Phone: 
- Email: 

**Hospital (Name):**

- Phone: 
- Email: 

**Pharmacy (Name):**

- Phone: 
- Email: 

**Emergency (Name):**

- Phone: 
- Email: 

Please see pages 18-23 and accompanying full Prescribing Information for Important Safety Information, including BOXED WARNINGS.
Use this space to write down additional information or questions.

Notes: ______________________________________________________

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For more information, visit GAZYVA.com

Images in this brochure do not depict actual patients.

Please see pages 18-23 and accompanying full Prescribing Information for Important Safety Information, including BOXED WARNINGS.

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GAZYVA® (obinutuzumab) injection, for intravenous use

Initial U.S. Approval: 2013

WARNING: HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

See full prescribing information for complete boxed warning.

• Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)
• Progressive Multifocal Leukoencephalopathy (PML) resulting in death. (5.2)

RECENT MAJOR CHANGES

Indications and Usage, Follicular Lymphoma (1.2) 11/2017
Dosage and Administration (2) 11/2017
Warnings and Precautions (5.3, 5.4, 5.6, 5.8) 11/2017
Contraindications (4) 11/2017

INDICATIONS AND USAGE

GAZYVA (obinutuzumab) is a CD20-directed cytolytic antibody and is indicated:
• in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia. (1, 14)
• in combination with bendamustine followed by GAZYVA monotherapy, for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen. (1, 14)
• in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, for the treatment of adults patients with previously untreated stage II bulky, III or IV follicular lymphoma. (1, 14)

DOSAGE AND ADMINISTRATION

• Premedicate for infusion reactions and tumor lysis syndrome. (2.2, 5.3, 5.4)
• Dilute and administer as intravenous infusion. Do not administer as an intravenous push or bolus. (2.1)
• The dose for chronic lymphocytic leukemia is 100 mg on day 1 and 900 mg on day 2 of Cycle 1, 1000 mg on day 8 and 15 of Cycle 1, and 1000 mg on day 1 of Cycles 2–6. (2.1)
• The dose for follicular lymphoma is 1000 mg on day 1, 8 and 15 of Cycle 1, 1000 mg on day 1 of Cycles 2–6 or Cycles 2–8, and then 1000 mg every 2 months for up to 2 years. (2.1)

DOSAGE FORMS AND STRENGTHS

1000 mg/40 mL (25 mg/mL) single-dose vial. (3)

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

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*Sections or subsections omitted from the full prescribing information are not listed.

GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or any of the excipients, including serum sickness with prior obinutuzumab use. (4)

WARNINGS AND PRECAUTIONS

• Infusion Reactions: Premedicate patients with glucocorticoid, acetaminophen, and anti-histamine. Monitor patients closely during infusions. Interrupt or discontinue infusion for reactions. (2.2, 5.3)
• Hypersensitivity Reactions Including Serum Sickness: Discontinue GAZYVA permanently. (5.3)
• Tumor Lysis Syndrome: Anticipate tumor lysis syndrome; premedicate with anti-hyperuricemics and adequate hydration especially for patients with high tumor burden, high circulating lymphocyte count or renal impairment. Correct electrolyte abnormalities, provide supportive care, and monitor renal function and fluid balance. (5.4)
• Infections: Monitor for infection during and after treatment. (5.5)
• Neutropenia: Monitor for infection and promptly treat. (5.6)
• Thrombocytopenia: Monitor platelet counts and for bleeding. Management of hemorrhage may require blood product support. (5.7)
• Immunization: Do not administer live virus vaccines prior to or during GAZYVA treatment. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥10% and ≥2% greater in the GAZYVA treated arm) were:
• Previously untreated CLL: infusion reactions, neutropenia, thrombocytopenia and diarrhea. (6)
• Relapsed or refractory NHL: infusion reactions, neutropenia, cough, constipation, pyrexia, upper respiratory tract infection, arthralgia, sinusitis, asthma and urinary tract infection. (6)
• Previously untreated NHL: infusion reactions, neutropenia, upper respiratory tract infection, cough, constipation, diarrhea, headache, herpesvirus infection, arthralgia, insomnia, pneumonitis, thrombocytopenia, decreased appetite, alopecia and puritus. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

• Pregnancy: Likely to cause fetal B-cell depletion. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2017
FULL PRESCRIBING INFORMATION

WARNING: 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 [see Warnings and Precautions (5.1)].
- Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

GAZYVA, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia [see Clinical Studies (14.1)].

1.2 Follicular Lymphoma (FL)

GAZYVA, in combination with bendamustine followed by GAZYVA monotherapy, is indicated for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen [see Clinical Studies (14.2)].

GAZYVA, in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, is indicated for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage Regimen

- Premedicate before each infusion [see Dosage and Administration (2.2)].
- Provide prophylactic hydration and anti-hyperuricemics to patients at high risk of tumor lysis syndrome [see Dosage and Administration (2.2) and Warnings and Precautions (5.4)].
- Administer only as an intravenous infusion through a dedicated line [see Dosage and Administration (2.6)].
- 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 reactions that can be fatal if they occur [see Warnings and Precautions (5.3)].

Chronic Lymphocytic Leukemia

Each dose of GAZYVA is 1000 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).
Table 1  Dose of GAZYVA to be Administered During Six 28-Day Treatment Cycles for Patients with CLL

<table>
<thead>
<tr>
<th>Day of treatment cycle</th>
<th>Dose of GAZYVA</th>
<th>Rate of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>100 mg</td>
<td>Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.</td>
</tr>
<tr>
<td>Day 2</td>
<td>900 mg</td>
<td>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.</td>
</tr>
<tr>
<td>Day 8</td>
<td>1000 mg</td>
<td>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.</td>
</tr>
<tr>
<td>Day 15</td>
<td>1000 mg</td>
<td>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.</td>
</tr>
</tbody>
</table>

If a planned dose of GAZYVA is missed, administer the missed dose as soon as possible and adjust dosing schedule to maintain the time interval between doses. If appropriate, patients who do not complete the Day 1 Cycle 1 dose may proceed to the Day 2 Cycle 1 dose.

**Follicular Lymphoma**

Each dose of GAZYVA is 1000 mg administered intravenously according to Table 2.

For patients with relapsed or refractory FL, administer GAZYVA in combination with bendamustine in six 28-day cycles. Patients who achieve stable disease, complete response, or partial response to the initial 6 cycles should continue on GAZYVA 1000 mg as monotherapy for up to two years.

For patients with previously untreated FL, administer GAZYVA with one of the following chemotherapy regimens:

- Six 28-day cycles in combination with bendamustine
- Six 21-day cycles in combination with CHOP, followed by 2 additional 21-day cycles of GAZYVA alone
- Eight 21-day cycles in combination with CVP

Patients with previously untreated FL who achieve a complete response or partial response to the initial 6 or 8 cycles should continue on GAZYVA 1000 mg as monotherapy for up to two years.
Table 2  Dose of GAZYVA to be Administered During 6-8 Treatment Cycles, Followed by GAZYVA Monotherapy for Patients with FL

<table>
<thead>
<tr>
<th>Day of treatment cycle</th>
<th>Dose of GAZYVA</th>
<th>Rate of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cycle 1 (loading doses)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1000 mg</td>
<td>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.</td>
</tr>
<tr>
<td>Day 8</td>
<td>1000 mg</td>
<td>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.</td>
</tr>
<tr>
<td>Day 15</td>
<td>1000 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Cycles 2–6 or 2–8</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>1000 mg</td>
<td>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.</td>
</tr>
<tr>
<td>Every two months for up to two years</td>
<td>1000 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 cycles. During monotherapy, maintain the original dosing schedule for subsequent doses. Monotherapy should be initiated approximately two months after the last dose of GAZYVA administered during the induction phase.

Management of Infusion Reactions in CLL and FL Patients

If a patient with CLL or FL experiences an infusion reaction of any grade during infusion, adjust the infusion as follows [see Warnings and Precautions (5.3)]:

- **Grade 4 (life-threatening):** Stop infusion immediately and permanently discontinue GAZYVA therapy.
  - For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further.

- **Grade 3 (severe):** 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 infusion reaction occurred) and, if patient does not experience any further infusion reaction 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 infusion-related symptom at rechallenge.
  - For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further.

- **Grade 1–2 (mild to moderate):** Reduce infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.
  - For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further.

2.2 Recommended Premedication for Infusion Reactions

Premedication to reduce the risk of infusion reactions is outlined in Table 3 [see Warnings and Precautions (5.3)].
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 [see Warnings and Precautions (5.3)].

Table 3  Premedication for GAZYVA Infusion to Reduce Infusion-Related Reactions (IRR)

<table>
<thead>
<tr>
<th>Day of Treatment Cycle</th>
<th>Patients requiring premedication</th>
<th>Premedication</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1: CLL</td>
<td>All patients</td>
<td>Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone(^1,2)</td>
<td>Completed at least 1 hour prior to GAZYVA infusion.</td>
</tr>
<tr>
<td>Day 1, Day 2</td>
<td></td>
<td>650–1000 mg acetaminophen</td>
<td>At least 30 minutes before GAZYVA infusion.</td>
</tr>
<tr>
<td>FL</td>
<td></td>
<td>anti-histamine (e.g., 50 mg diphenhydramine)</td>
<td></td>
</tr>
<tr>
<td>All subsequent infusions, CLL or FL</td>
<td>All patients</td>
<td>650–1000 mg acetaminophen</td>
<td>At least 30 minutes before GAZYVA infusion.</td>
</tr>
<tr>
<td></td>
<td>Patients with an IRR (Grade 1-2) with the previous infusion</td>
<td>650–1000 mg acetaminophen</td>
<td>At least 30 minutes before GAZYVA infusion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anti-histamine (e.g., 50 mg diphenhydramine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with a Grade 3 IRR with the previous infusion OR with a lymphocyte count &gt; 25 x 10⁹/L prior to next treatment</td>
<td>Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone(^1)</td>
<td>Completed at least 1 hour prior to GAZYVA infusion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>650–1000 mg acetaminophen</td>
<td>At least 30 minutes before GAZYVA infusion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anti-histamine (e.g., 50 mg diphenhydramine)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions.

\(^2\) 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.

2.3  Tumor Lysis Syndrome Prophylaxis

Patients with high tumor burden, high circulating absolute lymphocyte counts (greater than 25 x 10⁹/L) or renal impairment are considered at risk of tumor lysis syndrome and should receive prophylaxis. Premedicate with anti-hyperuricemics (e.g., allopurinol or rasburicase) and ensure adequate hydration prior to start of GAZYVA therapy. Continue prophylaxis prior to each subsequent GAZYVA infusion, as needed [see Warnings and Precautions (5.4)].
2.4 Antimicrobial Prophylaxis
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. Antiviral and antifungal prophylaxis should be considered.

2.5 Treatment Interruption for Toxicity
Consider treatment interruption if patients experience an infection, Grade 3 or 4 cytopenia, or a ≥ Grade 2 non-hematologic toxicity.

2.6 Preparation and Administration

Preparation
Prepare the solution for infusion, using aseptic technique, as follows:
- Inspect visually for any particulate matter and discoloration prior to administration.
- Dilute into a 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag. Do not use other diluents such as dextrose (5%).

Chronic Lymphocytic Leukemia
- Preparation of solution for infusion on day 1 (100 mg) and day 2 (900 mg) of Cycle 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.
- Preparation of solution for infusion on day 8 and 15 of Cycle 1 and day 1 Cycles 2–6:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 40 mL (1000 mg) into a 250 mL 0.9% sodium chloride infusion bag.

Follicular Lymphoma
- Preparation of solution for infusion:
  - Withdraw 40 mL of GAZYVA solution from the vial.
  - Dilute 40 mL (1000 mg) into a 250 mL 0.9% sodium chloride infusion bag.

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

Administration for CLL and FL Patients
- Administer as an intravenous infusion only.
- Do not administer as an intravenous push or bolus.
- Do not mix GAZYVA with other drugs.
- No incompatibilities between GAZYVA and polyvinylchloride (PVC) or non-PVC polyolefin bags and administration sets have been observed [see How Supplied/Storage and Handling (16.1)].

3 DOSAGE FORMS AND STRENGTHS
1000 mg/40 mL (25 mg/mL) single-dose vial.
4 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 [see Warnings and Precautions Section (5.4)].

5 WARNINGS AND PRECAUTIONS
5.1 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 such as GAZYVA. HBV reactivation has 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 has also 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 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, i.e., 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 physicians 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. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

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 physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming GAZYVA in patients who develop HBV reactivation.

5.2 Progressive Multifocal Leukoencephalopathy
JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed 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.

5.3 Infusion Reactions
GAZYVA can cause severe and life-threatening infusion reactions. Sixty-five percent of patients with CLL experienced a reaction to the first 1000 mg of GAZYVA infused. Thirty-eight 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. Infusion reactions can also occur with subsequent infusions. 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 [see Adverse Reactions (6.1)].
Premedicate patients with acetaminophen, antihistamine, and a glucocorticoid. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for infusion reactions as needed. Closely monitor patients during the entire infusion. Infusion reactions within 24 hours of receiving GAZYVA have occurred [see Dosage and Administration (2)].

For patients with any Grade 4 infusion reactions, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction: Stop the GAZYVA infusion. Permanently discontinue GAZYVA therapy.

For patients with Grade 1, 2, or 3 infusion reactions: Interrupt GAZYVA for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms [see Dosage and Administration (2)].

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 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 as is suggested here.

5.4 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, the infusion must be stopped and treatment permanently discontinued. Patients with known hypersensitivity reactions to GAZYVA, including serum sickness, must not be retreated.

5.5 Tumor Lysis Syndrome
Tumor lysis syndrome (TLS), including fatal cases, has been reported in patients receiving GAZYVA. Patients with high tumor burden, high circulating lymphocyte count (> 25 x 10⁹/L) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of GAZYVA [see Dosage and Administration (2.3)].

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.

5.6 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 [see Adverse Reactions (6.1)]. 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.
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.

5.7 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 administration of granulocyte colony-stimulating factors (GCSF) in patients with 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).

Consider dose delays in the case of Grade 3 or 4 neutropenia. 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.

5.8 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 and CLL 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 subsequent 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, which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

5.9 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.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Hepatitis B virus reactivation [see Warnings and Precautions (5.1)]
- Progressive multifocal leukoencephalopathy [see Warnings and Precautions (5.2)]
- Infusion reactions [see Warnings and Precautions (5.3)]
- Hypersensitivity reactions including serum sickness [see Warnings and Precautions (5.4)]
- Tumor lysis syndrome [see Warnings and Precautions (5.5)]
- Infections [see Warnings and Precautions (5.6)]
- Neutropenia [see Warnings and Precautions (5.7)]
- Thrombocytopenia [see Warnings and Precautions (5.8)]
6.1 Clinical Trial Experience

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 practice.

Summary of Clinical Trial Experience in Chronic Lymphocytic Leukemia

The data described in Tables 4-5 below are based on a safety population of 773 previously untreated patients with CLL in the CLL11 study. Patients were treated with chlorambucil alone, GAZYVA in combination with chlorambucil, or rituximab product in combination with chlorambucil. The Stage 1 analysis compared GAZYVA in combination with chlorambucil vs. chlorambucil alone, and Stage 2 compared GAZYVA in combination with chlorambucil vs. rituximab product in combination with chlorambucil. Adverse reactions rates and laboratory abnormalities from the Stage 2 phase are presented below and 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 obinutuzumab 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 obinutuzumab with similar incidences of Grade 3 to 4 abnormalities between the two arms.

Patients received three 1000 mg doses of GAZYVA on the first cycle and a single dose of 1000 mg once every 28 days for 5 additional cycles in combination with chlorambucil (6 cycles of 28 days each in total). In the last 140 patients enrolled, the first dose of GAZYVA was split between day 1 (100 mg) and day 2 (900 mg) [see Dosage and Administration (2.1)]. In total, 81% of patients received all 6 cycles (of 28 days each) of GAZYVA-based therapy.

The most common adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVA containing arm were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, nausea, and diarrhea.

The most common Grade 3 to 4 adverse reactions (incidence ≥10%) observed in patients with CLL in the GAZYVA containing arm were neutropenia, infusion reactions, thrombocytopenia, anemia, pyrexia, cough, nausea, and diarrhea.

Table 4 Summary of Adverse Reactions Reported in ≥5% of Patients with CLL and at Least 2% Greater in the GAZYVA Treated Arm (Stage 2)

<table>
<thead>
<tr>
<th>Body System Adverse Reactions</th>
<th>GAZYVA + Chlorambucil n = 336</th>
<th>Rituximab product + Chlorambucil n = 321</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 to 4 %</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion Related Reaction</td>
<td>66</td>
<td>20</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

* Adverse reactions reported under “Blood and lymphatic system disorders” reflect those reported by investigator as clinically significant.
Table 5  Post-Baseline Laboratory Abnormalities by CTCAE Grade in ≥ 5% of Patients with CLL and at Least 2% Greater in the GAZYVA Treated Arm (Stage 2)

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>GAZYVA + Chlorambucil n = 336</th>
<th>Rituximab product + Chlorambucil n = 321</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 to 4 %</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>76</td>
<td>46</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>80</td>
<td>39</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>84</td>
<td>35</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>48</td>
<td>13</td>
</tr>
<tr>
<td>Anemia</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>AST/SGOT increased</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>ALT/SGPT increased</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>23</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Summary of Clinical Trial Experience in Non-Hodgkin Lymphoma

**GADOLIN**

The GADOLIN study evaluated safety in 392 patients with relapsed or refractory NHL, including FL (81%), small lymphocytic lymphoma and marginal zone lymphoma (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 the population of patients with FL, the profile of adverse reactions was consistent with the overall NHL population. Patients were treated with either GAZYVA in combination with bendamustine, followed by GAZYVA monotherapy in patients that have not progressed, or with bendamustine alone.

Patients randomized to the GAZYVA + bendamustine arm received three weekly 1000 mg doses of GAZYVA in the first cycle and a single dose of 1000 mg once every 28 days for 5 additional cycles in combination with bendamustine 90 mg/m² on Days 1 and 2 in all 6 cycles. Patient randomized to the bendamustine alone arm received 120 mg/m² on Days 1 and 2. This regimen continued for 6 cycles of 28 days in duration. For patients who did not progress on GAZYVA in combination with bendamustine, a single dose of 1000 mg GAZYVA monotherapy was given every two months until progression or for a maximum of two years. During combination therapy with GAZYVA and bendamustine, 79% of patients received all 6 treatment cycles of GAZYVA and 76% received all 6 treatment cycles of bendamustine compared to 67% of patients in the bendamustine alone arm.

The most common adverse reactions (incidence ≥ 10%) observed in GADOLIN in the GAZYVA containing arm were infusion reactions, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, anemia, asthenia and urinary tract infection.

The most common Grade 3 to 4 adverse reactions (incidence ≥ 10%) observed in GADOLIN in the GAZYVA containing arm were neutropenia, thrombocytopenia and infusion reactions.
Table 6  Summary of Adverse Reactions Reported in ≥ 5% of Patients with Relapsed or Refractory NHL and at Least 2% Greater in the GAZYVA plus Bendamustine Followed by GAZYVA Monotherapy Treated Arm (GADOLIN)

<table>
<thead>
<tr>
<th>Body System Adverse Reactions</th>
<th>GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 194</th>
<th>Bendamustine n = 198</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 to 4 %</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>Infusion Related Reaction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Neutropenia</td>
<td>35</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Constipation</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>5</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Pyrexia</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>11</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Upper Respiratory Tract Infection</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Urinary Tract Infection</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>9</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Pain in Extremity</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Cough</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Nasal Congestion</td>
<td>7</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Pruritus</td>
<td>9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined as any related adverse reaction that occurred during or within 24 hours of infusion.

During the monotherapy period with GAZYVA, the most common adverse reactions (incidence ≥ 5%) in GADOLIN were cough (15%), upper respiratory tract infections (12%), neutropenia (11%), sinusitis (10%), diarrhea (8%), infusion related reactions (8%), nausea (8%), fatigue (8%), bronchitis (7%), arthralgia (7%), pyrexia (6%), nasopharyngitis (6%), and urinary tract infection (6%). Grade 3 to 4 adverse reactions during the monotherapy period included neutropenia (10%) and, at 1% each, anemia, febrile neutropenia, thrombocytopenia, sepsis, upper respiratory tract infection, and urinary tract infection.

Table 7  Post-Baseline Laboratory Abnormalities by CTCAE Grade in ≥ 5% of Patients with Relapsed or Refractory NHL and at Least 2% Greater in the GAZYVA plus Bendamustine Followed by GAZYVA Monotherapy Treated Arm<sup>a</sup> (GADOLIN)

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 194</th>
<th>Bendamustine n = 198</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 to 4 %</td>
</tr>
<tr>
<td>Hematology</td>
<td>Neutropenia</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>99</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Hypocalcemia</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia</td>
<td>41</td>
</tr>
</tbody>
</table>
In the monotherapy phase of treatment with GAZYVA, the most frequently reported hematological laboratory abnormalities (incidence ≥ 20%) were lymphopenia (80%), leukopenia (63%), low hemoglobin (50%), neutropenia (46%) and thrombocytopenia (35%). The most frequently reported hematological Grade 3 to 4 laboratory abnormalities (incidence ≥ 1%) during the monotherapy period were lymphopenia (52%), neutropenia (27%), leukopenia (20%) and thrombocytopenia (4%).

In the monotherapy phase of treatment with GAZYVA, the most frequently reported chemistry laboratory abnormalities (incidence ≥ 20%) were elevated creatinine (69%), decreased creatinine clearance (CrCl; 43%), hypophosphatemia (25%), AST/SGOT increased (24%) and ALT/SGPT increased (21%). The most frequently reported chemistry Grade 3 to 4 laboratory abnormalities (incidence ≥ 1%) during the monotherapy period were hypophosphatemia (5%), hyponatremia (3%) and decreased CrCl (1%).

**GALLIUM**

A randomized, open-label multicenter trial (GALLIUM) evaluated the safety of GAZYVA as compared to rituximab product in 1385 patients with previously untreated follicular lymphoma (86%) or marginal zone lymphoma (14%). Patients received chemotherapy (bendamustine, CHOP, or CVP) combined with either GAZYVA (691 patients) or rituximab product (694 patients), followed in responding patients by GAZYVA or rituximab product monotherapy every two months until disease progression or for a maximum of two years. The study excluded patients having an absolute neutrophil count (ANC) < 1500 / µL, platelets < 75,000 / µL, CrCl < 40 mL/min and, unless attributable to lymphoma, hepatic transaminases > 2.5 x upper limit of normal.

The median age was 60 (range: 23-88), 47% were male, 82% were white, and 97% had an ECOG performance status of 0 or 1. The chemotherapy was bendamustine in 59%, CHOP in 31% and CVP in 10% of patients. Following combination therapy, 624 patients (90%) in the GAZYVA arm and 612 patients (88%) in the rituximab product arm received monotherapy.

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.

During combination therapy, 93% of patients received all treatment cycles in the GAZYVA arm, and 92% received all treatment cycles in the rituximab product arm. Of the responding patients who began monotherapy with GAZYVA or rituximab product, 76% and 73%, respectively, completed the full course. Dose modification due to adverse reactions occurred in 74% of the GAZYVA arm and 63% of the rituximab product arm throughout study treatment, and discontinuation of any study drug due to adverse reactions occurred in 18% and 15%, respectively.

Throughout treatment and follow-up, the most common adverse reactions (incidence ≥ 20%) observed at least 2% more in the GAZYVA arm included infusion related reactions, neutropenia, upper respiratory tract infection, cough, constipation and diarrhea (Table 8). 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.

| **Table 8** Common Adverse Reactions (≥ 10% Incidence and ≥ 2% Greater in the GAZYVA Arm) in Patients with Previously Untreated NHL (GALLIUM) |
|-----------------|---|---|---|---|
| **4 Lab Abnormalities.** |
| Alt/SGPT increased | 35 | 1 | 31 | 4 |
| Elevated creatinine | 87 | 4 | 92 | 2 |
| Creatinine clearance decreased | 58 | 6 | 61 | 4 |

* Two percent different in either the All Grades or Grade 3 to 4 Lab Abnormalities.
<table>
<thead>
<tr>
<th>Body System Adverse Reactions</th>
<th>GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 691</th>
<th>Rituximab product + chemotherapy followed by rituximab product monotherapy n = 694</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 to 5 %</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion Related Reaction a, b</td>
<td>72</td>
<td>12</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia d</td>
<td>53</td>
<td>49</td>
</tr>
<tr>
<td>Thrombocytopenia d</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Herpesvirus Infection</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>35</td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>32</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>15</td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>14</td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

a Includes adverse reactions reported throughout study treatment and follow-up.
b Includes grouped preferred terms.
c Except where noted, individual events that meet the definition of “infusion related reaction” are excluded from Table 8 above, as they are already included in the group term “Infusion Related Reaction”. The most common individual terms within the group term “Infusion Related Reaction” in decreasing order of frequency are nausea, chills, pyrexia and vomiting.
d Includes adverse reactions reported as infusion related reactions.

tInfusion related reactions are defined as any related adverse reaction that occurred during or within 24 hours of infusion.
Neutropenia includes neutropenia, agranulocytosis, febrile neutropenia, granulocytopenia and neutrophil count decreased; febrile neutropenia includes febrile neutropenia, neutropenic infection, neutropenic sepsis, and febrile bone marrow aplasia.
Thrombocytopenia includes thrombocytopenia and platelet count decreased.
Upper respiratory tract infection includes upper respiratory tract congestion, upper respiratory tract inflammation, sinusitis bacterial, upper respiratory tract infection bacterial, pharyngitis streptococcal, sinusitis fungal, upper respiratory fungal infection, acute sinusitis, chronic sinusitis, laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, rhinovirus infection, viral pharyngitis, viral rhinitis, viral upper respiratory tract infection.
Herpesvirus infection includes genital herpes, genital herpes zoster, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes simplex pharyngitis, herpes virus infection, herpes zoster, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster oticus, nasal herpes, ophthalmic herpes simplex, ophthalmic herpes zoster, oral herpes, varicella, varicella zoster virus infection.
Pneumonia includes pneumonia bacterial, pneumonia haemophilus, pneumonia pneumococcal, pneumonia fungal, pneumocystis jiroveci infection, pneumocystis jiroveci pneumonia, atypical pneumonia, lung infection, pneumonia, pneumonia aspiration, lung infiltration.
Cough includes cough, productive cough, upper-airway cough syndrome.
Diarrhea includes diarrhea, defecation urgency, frequent bowel movement, gastroenteritis, gastroenteritis viral.
Headache includes cluster headache, headache, sinus headache, tension headache, migraine.
Insomnia includes initial insomnia, insomnia, sleep disorder.
Pruritus includes pruritus and pruritus generalized.
During the monotherapy period, the common adverse reactions (incidence ≥ 10%) observed at least 2% more with GAZYVA were upper respiratory tract infection (40%), cough (23%), musculoskeletal pain (20%), neutropenia (19%) and herpesvirus infection (13%).

Table 9 summarizes treatment-emergent laboratory abnormalities during treatment and follow-up. The Grade 3 to 4 abnormalities reported at least 2% more in the GAZYVA arm were lymphopenia, leukopenia, neutropenia, thrombocytopenia and hyperuricemia. Patients in the GAZYVA arm, as compared to the rituximab product arm, had higher incidences of Grade 4 neutropenia (38% vs. 30%, respectively), Grade 4 lymphopenia (33% vs. 22%), and Grade 4 leukopenia (17% vs. 12%).

### Table 9  Common New or Worsening Laboratory Abnormalities (≥ 10% Incidence and ≥ 2% Greater in the GAZYVA Arm) in Patients with Previously Untreated NHL (GALLIUM)

<table>
<thead>
<tr>
<th>Laboratory Abnormalities *</th>
<th>GAZYVA+ chemotherapy followed by GAZYVA monotherapy n = 691</th>
<th>Rituximab product + chemotherapy followed by rituximab product monotherapy n = 694</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 to 4 %</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>97</td>
<td>83</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>92</td>
<td>49</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>84</td>
<td>59</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>68</td>
<td>11</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/SGPT increased</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>AST/SGOT increased</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Hypoproteinemia</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>16</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

* Includes lab abnormalities, reported throughout treatment and follow-up, that were new or worsening, or worsening from baseline unknown.

In the monotherapy phase, new-onset Grade 3 or 4 neutropenia was reported in 21% of patients in the GAZYVA arm (Grade 4, 10%) and 17% of patients in the rituximab product arm (Grade 4, 9%).

**Infusion Reactions:**

**Chronic Lymphocytic Leukemia**

The incidence of infusion reactions in the CLL11 study was 65% with the first infusion of GAZYVA. The incidence of Grade 3 or 4 infusion reactions was 20% with 7% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3% with the second 1000 mg and < 1% thereafter. No Grade 3 or 4 infusion reactions were reported beyond the first 1000 mg infused.
Of the first 53 patients receiving GAZYVA in CLL11, 47 (89%) experienced an infusion reaction. After this experience, study protocol modifications were made to require pre-medication with a corticosteroid, antihistamine, and acetaminophen. The first dose was also divided into two infusions (100 mg on day 1 and 900 mg on day 2). For the 140 patients for whom these mitigation measures were implemented, 74 patients (53%) experienced a reaction with the first 1000 mg (64 patients on day 1, 3 patients on day 2, and 7 patients on both days) and <3% thereafter [see Dosage and Administration (2)].

**Non-Hodgkin Lymphoma**

Overall, 69% of patients in the GADOLIN study experienced an infusion reaction (all grades) during treatment with GAZYVA in combination with bendamustine. The incidence of Grade 3 to 4 infusion reactions in GADOLIN was 11%. In Cycle 1, the incidence of infusion reactions (all grades) was 55% in patients receiving GAZYVA in combination with bendamustine with Grade 3 to 4 infusion reactions reported in 9%. In patients receiving GAZYVA in combination with bendamustine, the incidence of infusion reactions was highest on Day 1 (38%), and gradually decreased on Days 2, 8 and 15 (25%, 7% and 4%, respectively).

During Cycle 2, the incidence of infusion reactions was 24% in patients receiving GAZYVA in combination with bendamustine and decreased with subsequent cycles.

During GAZYVA monotherapy in GADOLIN, infusion reactions (all grades) were observed in 8% of patients. No Grade 3 to 4 infusion reactions were reported during GAZYVA monotherapy.

Overall, 2% of patients in GADOLIN experienced an infusion reaction leading to discontinuation of GAZYVA.

In GALLIUM, 72% of patients in the GAZYVA treated arm experienced an infusion reaction (all grades). The incidence of Grade 3 to 4 infusion reactions for these patients was 12%. In Cycle 1, the incidence of infusion reactions (all grades) was 62% in the GAZYVA treated arm with Grade 3 to 4 infusion reactions reported in 10%. The incidence of infusion reactions (all grades) was highest on Day 1 (60%), and decreased on Days 8 and 15 (9% and 6%, respectively).

During Cycle 2, the incidence of infusion reactions (all grades) in the GAZYVA treated arm was 13% and decreased with subsequent cycles.

During GAZYVA monotherapy treatment in GALLIUM, infusion reactions (all grades) were observed in 9% of patients.

Overall, 1% of patients in GALLIUM experienced an infusion reaction leading to discontinuation of GAZYVA.

**Neutropenia:**

**Chronic Lymphocytic Leukemia**

The incidence of neutropenia reported as an adverse reaction in CLL11 was 38% in the GAZYVA treated arm and 32% in the rituximab product treated arm, with the incidence of serious adverse reactions being 1% and <1%, respectively (Table 4). Cases of late-onset neutropenia (occurring 28 days after completion of treatment or later) were 16% in the GAZYVA treated arm and 12% in the rituximab product treated arm.

**Non-Hodgkin Lymphoma**

The incidence of neutropenia in GADOLIN was higher in the GAZYVA plus bendamustine arm (38%) compared to the arm treated with bendamustine alone (32%). Cases of prolonged neutropenia (3%) and late onset neutropenia (7%) were also reported in the GAZYVA plus bendamustine arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with bendamustine (31%) compared to the GAZYVA monotherapy treatment phase (12%).
The incidence of neutropenia in GALLIUM was higher in the GAZYVA treated arm (53%) compared to the rituximab product treated arm (47%). Cases of prolonged neutropenia (1%) and late onset neutropenia (4%) were also reported in the GAZYVA treated arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with chemotherapy (45%) compared to the GAZYVA monotherapy treatment phase (20%).

Infection:

**Chronic Lymphocytic Leukemia**

The incidence of infections was similar between GAZYVA and rituximab product treated arms. Thirty-eight percent of patients in the GAZYVA treated arm and 37% in the rituximab product treated arm experienced an infection, with Grade 3 to 4 rates being 11% and 13%, respectively. Fatal events were reported in 1% of patients in both arms.

**Non-Hodgkin Lymphoma**

The incidence of infection in GADOLIN was 66% in the GAZYVA plus bendamustine arm and 56% in the bendamustine arm, with Grade 3 to 4 events reported in 16% and 14%, respectively. Fatal events were reported in 3% of patients in the GAZYVA plus bendamustine arm and 4% in the bendamustine arm.

The incidence of infections in GALLIUM was 82% in the GAZYVA treated arm and 73% in the rituximab product treated arm, with Grade 3 to 4 events reported in 21% and 17%, respectively. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to <1% in the rituximab product arm.

The incidence of Grade 3 to 4 infections in the GAZYVA and rituximab product treated arms was lower in patients receiving GCSF prophylaxis (14%; 16%) compared with patients not receiving GCSF prophylaxis (24%; 18%). The incidence of fatal infections in patients receiving GCSF prophylaxis in the GAZYVA and rituximab product treated arms was 2% and 0%, respectively, and was 2% and <1% in patients not receiving GCSF prophylaxis.

*Thrombocytopenia*:

**Chronic Lymphocytic Leukemia**

The overall incidence of thrombocytopenia reported as an adverse reaction was higher in the GAZYVA treated arm (14%) compared to the rituximab product treated arm (7%), with the incidence of Grade 3 to 4 events being 10% and 3%, respectively (Table 4). The difference in incidences between the treatment arms is driven by events occurring during the first cycle. The incidence of thrombocytopenia (all grades) in the first cycle was 11% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 4 rates being 8% and 2%, respectively. Four percent of patients in the GAZYVA treated arm experienced acute thrombocytopenia (occurring within 24 hours after the GAZYVA infusion).

The overall incidence of hemorrhagic events and the number of fatal hemorrhagic events were similar between the treatment arms, with 3 in the rituximab product and 4 in the GAZYVA treated arms. However, all fatal hemorrhagic events in patients treated with GAZYVA occurred in Cycle 1.

**Non-Hodgkin Lymphoma**

The incidence of thrombocytopenia in GADOLIN was lower in the GAZYVA plus bendamustine arm (15%) compared to the arm treated with bendamustine alone (24%). The incidence of hemorrhagic events in GAZYVA plus bendamustine treated patients compared to bendamustine alone was 11% and 10%, respectively. Grade 3 to 4 hemorrhagic events were similar in both treatment arms (5% in the GAZYVA plus bendamustine arm and 3% in the bendamustine arm).
In GALLIUM, thrombocytopenia was reported as an adverse reaction in 14% of the GAZYVA treated arm and 8% of the rituximab product treated arm, with the incidence of Grade 3 to 4 events being 7% and 3% respectively. The difference in incidences between the treatment arms is driven by events occurring during the first cycle. The incidence of thrombocytopenia (all grades) in the first cycle were 9% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 4 rates being 5% and 1%, respectively. In GALLIUM, both treatment arms had a 12% overall incidence of hemorrhagic events and a < 1% incidence of fatal hemorrhagic events.

**Tumor Lysis Syndrome:** The incidence of Grade 3 or 4 tumor lysis syndrome in GAZYVA treated patients was 2% in CLL11, 0.5% in GADOLIN and 0.9% in GALLIUM.

**Musculoskeletal Disorders:**

**Chronic Lymphocytic Leukemia**

Adverse reactions related to musculoskeletal disorders (all events from the body system), including pain, have been reported in the GAZYVA treated arm with higher incidence than in the rituximab product treated arm (18% vs. 15%).

**Non-Hodgkin Lymphoma**

In GADOLIN, adverse reactions related to musculoskeletal disorders (all events from the body system), including pain, have been reported in the GAZYVA plus bendamustine treated arm with higher incidence than in the bendamustine alone arm (41% vs. 29%).

In GALLIUM, musculoskeletal disorders were reported in 54% of patients in the GAZYVA treated arm and 49% of patients in the rituximab product treated arm.

**Liver Enzyme Elevations:** Hepatic enzyme elevations have occurred in CLL patients who received GAZYVA in clinical trials and had normal baseline hepatic enzyme levels (AST, ALT and ALP). The events occurred most frequently within 24–48 hours of the first infusion. In some patients, elevations in liver enzymes were observed concurrently with infusion reactions or tumor lysis syndrome. In the CLL11 study, there was no clinically meaningful difference in overall hepatotoxicity adverse reactions between all arms (4% of patients in the GAZYVA treated arm). Medications commonly used to prevent infusion reactions (e.g., acetaminophen) may also be implicated in these events. Monitor liver function tests during treatment, especially during the first cycle. Consider treatment interruption or discontinuation for hepatotoxicity.

**Gastrointestinal Perforation:** Cases of gastrointestinal perforation have been reported in patients receiving GAZYVA, mainly in NHL.

**Worsening of Pre-existing Cardiac Conditions:** Fatal cardiac events have been reported in patients treated with GAZYVA.

### 6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to GAZYVA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Seven percent (18/271) of patients with CLL tested positive for anti-GAZYVA antibodies at one or more time points in CLL11. No patients developed anti-GAZYVA antibodies during or following
GAZYVA treatment in GADOLIN, while 1 patient (1/564, 0.2%) developed anti-GAZYVA antibodies in GALLIUM. Neutralizing activity of anti-GAZYVA antibodies has not been assessed.

6.3 Postmarketing Safety Information

The following adverse reactions have been identified during post-approval use of GAZYVA.

- Immune/Autoimmune Events: Serum sickness

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

GAZYVA is likely to cause fetal B-cell depletion based on findings from animal studies and the drug’s mechanism of action [see Clinical Pharmacology (12.1)]. There are no data with GAZYVA use in pregnant women to inform a drug-associated risk. Monoclonal antibodies are transferred across the placenta. In animal reproduction studies, weekly intravenous administration of obinutuzumab to pregnant cynomolgus monkeys from day 20 of pregnancy until parturition which includes the period of organogenesis at doses with exposures up to 2.4 times the exposure at the clinical dose of 1000 mg monthly produced opportunistic infections and immune complex mediated hypersensitivity reactions. No embryo-toxic or teratogenic effects were observed in the monkeys (see Data). Consider the potential risk to the fetus when prescribing GAZYVA to a pregnant woman.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

GAZYVA is likely to cause fetal B-cell depletion (see Data). Avoid administering live vaccines to neonates and infants exposed to GAZYVA in utero until B-cell recovery occurs [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.2)].

Data

Animal Data

In a pre- and post-natal development study, pregnant cynomolgus monkeys received weekly intravenous doses of 25 or 50 mg/kg obinutuzumab from day 20 of pregnancy until parturition, which includes the period of organogenesis. The high dose results in an exposure (AUC) that is 2.4 times the exposure in patients with CLL at the recommended label dose. There were no embryo-toxic or teratogenic effects in animals. Secondary opportunistic infections, immune complex mediated hypersensitivity reactions, or a combination of both were observed in exposed dams. When first measured on day 28 postpartum, obinutuzumab was detected in offspring at levels in the range of maternal serum levels on the same day, and B-cells were completely depleted. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months after birth.

Obinutuzumab was measured in the milk of lactating cynomolgus monkeys on day 28 postpartum after weekly intravenous administration from day 20 of pregnancy until parturition. Concentrations in milk were approximately 0.04% and 0.13% of concentrations in maternal serum in the 25 and 50 mg/kg groups, respectively.
8.2 Lactation
Risk Summary

There is no information regarding the presence of GAZYVA in human milk, the effects on the breastfed child, or the effects on milk production. However, low levels of obinutuzumab were present in the milk of lactating cynomolgus monkeys [see Use in Specific Populations (8.1)]. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and child circulations in substantial amounts. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for GAZYVA and any potential adverse effects on the breastfed child from GAZYVA or from the underlying maternal condition.

8.4 Pediatric Use
The safety and effectiveness of GAZYVA in pediatric patients have not been established.

8.5 Geriatric Use
Chronic Lymphocytic Leukemia

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 [see Clinical Studies (14.1)].

Non-Hodgkin Lymphoma

Of 194 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, 52% of patients experienced serious adverse reactions and 26% experienced adverse reactions leading to treatment withdrawal while in patients under 65, 28% and 12% 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 in GALLIUM.

10 OVERDOSAGE

There has been no experience with overdose in human clinical trials. For patients who experience overdose, treatment should consist of immediate interruption or reduction of GAZYVA and supportive therapy.

11 DESCRIPTION

GAZYVA (obinutuzumab) is a humanized anti-CD20 monoclonal antibody of the IgG1 subclass. It recognizes a specific epitope of the CD20 molecule found on B cells. The molecular mass of the antibody is approximately 150 kDa.

GAZYVA is produced by mammalian cell (CHO) suspension culture. GAZYVA was engineered for reduced fucose content as compared to a typical IgG1 produced in CHO cells. GAZYVA is a sterile, clear, colorless to slightly brown, preservative-free liquid concentrate for intravenous administration. GAZYVA is supplied at a concentration of 25 mg/mL in 1000 mg single-dose vials. The product is
formulated in 20 mM L-histidine/L-histidine hydrochloride, 240 mM trehalose, 0.02% poloxamer 188. The pH is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. Upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways (direct cell death), and/or (3) activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis.

As an antibody with reduced fucose content, obinutuzumab induces greater ADCC activity than rituximab in vitro using human cancer cell lines. Obinutuzumab also demonstrated an increased ability to induce direct cell death when compared to rituximab. Obinutuzumab binds to FcγRIII using purified proteins with a higher affinity than rituximab. Obinutuzumab and rituximab bind with similar affinity to overlapping epitopes on CD20.

12.2 Pharmacodynamics
In patients with CLL, GAZYVA caused CD19 B-cell depletion (defined as CD19 B cell counts < 0.07 x 10⁹/L). Initial CD19 B cell recovery was observed in some patients approximately 9 months after the last GAZYVA dose. At 18 months of follow-up, some patients remain B cell depleted.

Although the depletion of B cells in the peripheral blood is a measurable pharmacodynamic effect, it is not directly correlated with the depletion of B-cells in solid organs or in malignant deposits. B cell depletion has not been shown to be directly correlated to clinical response.

Cardiac Electrophysiology
The potential effects of GAZYVA on the QTc interval have not been studied.

12.3 Pharmacokinetics
The pharmacokinetic parameters of obinutuzumab after 100 mg on day 1 and 900 mg on day 2 of Cycle 1, 1000 mg on day 8 and 15 of Cycle 1, and 1000 mg on day 1 of Cycles 2–6 for CLL and after 1000 mg on day 1, 8 and 15 of Cycle 1, 1000 mg on day 1 of Cycles 2-6 or Cycles 2-8, and then 1000 mg every 2 months for up to 2 years for NHL are provided in Table 10. The dosing regimen is within the linear pharmacokinetic behavior of obinutuzumab.

<table>
<thead>
<tr>
<th>Table 10</th>
<th>Obinutuzumab Measures of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK Measure</td>
<td>CLL&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cmax, µg/mL</td>
<td>466.3 (35)</td>
</tr>
<tr>
<td>Ctrough, µg/mL</td>
<td>192.5 (78)</td>
</tr>
<tr>
<td>AUC, µg/mL*day</td>
<td>8701 (51)</td>
</tr>
</tbody>
</table>

Results are presented as geometric mean (% Coefficient of Variation).

<sup>a</sup> Induction Cycle 6 of a 28-day cycle;  
<sup>b</sup> Induction Cycle 8 of a 21-day cycle.

Elimination
The elimination of obinutuzumab is comprised of a linear clearance pathway and a time-dependent non-linear clearance pathway. As GAZYVA treatment progresses, the impact of the time-dependent
pathway diminishes in a manner suggesting target-mediated drug disposition (TMDD) and saturation of the TMDD at the end of the treatment cycle at the proposed clinical dose regimen. The pharmacokinetic properties of obinutuzumab in patients with CLL and NHL are provided in Table 11.

### Table 11 Pharmacokinetic Parameters of Obinutuzumab

<table>
<thead>
<tr>
<th></th>
<th>CLL</th>
<th>NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of Distribution&lt;sup&gt;a&lt;/sup&gt;, L</td>
<td>4.1 (20)</td>
<td>4.3 (21)</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal Half-life, days</td>
<td>25.5 (48)</td>
<td>35.3 (35)</td>
</tr>
<tr>
<td>Clearance, L/day</td>
<td>0.11 (53)</td>
<td>0.08 (41)</td>
</tr>
</tbody>
</table>

Parameters are presented as geometric mean (% Coefficient of Variation).

<sup>a</sup> At steady state.

**Specific Populations**

Age (median [range]: 63 [22, 89] years) and baseline creatinine clearance (CrCL) (median [range] 84 [22, >120] mL/min) did not affect the pharmacokinetics of GAZYVA. In patients with CrCL \( \leq 30 \) mL/min, the pharmacokinetics of GAZYVA was unaffected. GAZYVA has not been studied in patients with hepatic impairment.

The volume of distribution and steady-state clearance increased with body weight; however, the expected change in exposure does not warrant a dose modification.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with obinutuzumab.

No specific studies have been conducted to evaluate potential effects on fertility; however, no adverse effects on male or female reproductive organs were observed in the 26-week repeat-dose toxicity study in cynomolgus monkeys.

### 14 CLINICAL STUDIES

#### 14.1 Chronic Lymphocytic Leukemia

GAZYVA was evaluated in a three-arm, open-label, active-controlled, randomized, multicenter trial (CLL11; NCT01010061) in 781 patients with previously untreated CD20+ CLL requiring treatment who had coexisting medical conditions or reduced renal function as measured by creatinine clearance (CrCl) < 70 mL/min. Patients with CrCl < 30 mL/min, active infections, positive hepatitis B (HBsAg or anti-HBc positive; patients positive for anti-HBc could be included if hepatitis B viral DNA was not detectable) and hepatitis C serology, or immunization with live virus vaccine within 28 days prior to randomization were excluded from the trial. Patients were treated with chlorambucil control (Arm 1), GAZYVA in combination with chlorambucil (Arm 2), or rituximab product in combination with chlorambucil (Arm 3). The safety and efficacy of GAZYVA was evaluated in a Stage 1 comparison of Arm 1 vs. Arm 2 in 356 patients and a Stage 2 comparison of Arm 2 vs. Arm 3 in 663 patients.

The majority of patients received 1000 mg of GAZYVA on days 1, 8 and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of GAZYVA was divided between day 1 (100 mg) and day 2 (900 mg) [see Dosage and
Administration (2.1)], which was implemented in 140 patients. Chlorambucil was given orally at 0.5 mg/kg on day 1 and day 15 of all treatment cycles (1 to 6).

In CLL11, the median age was 73 years, 62% were male, and 95% were Caucasian. Sixty-five percent had a CrCl < 70 mL/min and 76% had multiple coexisting medical conditions. Twenty-two percent of patients were Binet stage A, 42% were stage B, and 36% were stage C. The median estimated CrCl was 62 mL/min. Eighty-one percent of patients treated with GAZYVA in combination with chlorambucil received all 6 cycles compared to 89% of patients in the rituximab product treated arm and 67% in the chlorambucil alone arm.

In the Stage 1 analysis of CLL11, the median progression-free survival (PFS) in the GAZYVA in combination with chlorambucil arm was 27.2 months and 11.2 months in the chlorambucil alone arm (median observation time 22.8 months) as assessed by independent review and is consistent with investigator-assessed PFS. The median overall survival (OS) was not yet reached with a total of 46 deaths: 22 (9%) in the GAZYVA in combination with chlorambucil arm and 24 (20%) in the chlorambucil arm. The hazard ratio for OS was 0.41 (95% CI: 0.23-0.74).

In the Stage 2 analysis of CLL11, the median PFS was 26.7 months in the GAZYVA arm and 14.9 months in the rituximab product arm with a median observation time of 18.7 months (HR: 0.42, 95% CI: 0.33-0.54, p-value < 0.0001). These results were assessed by independent review and are consistent with investigator-assessed PFS. Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The cutoff for a negative status was one CLL cell per 10^4 leukocytes in the sample (i.e., an MRD value of < 10^4 was considered negative). Among patients who achieved complete response (CR) and complete response with incomplete marrow recovery (CRi; 94 patients in the GAZYVA arm and 34 patients in the rituximab product arm), 18 patients (19%) had negative MRD in the bone marrow in the GAZYVA arm compared to 2 patients (6%) in the rituximab product arm. Out of the patients who achieved CR and CRi, 39 patients (41%) in the GAZYVA arm, and 4 patients (12%) in the rituximab product arm were MRD negative in peripheral blood samples collected at least 3 months after the end of treatment.

Efficacy results are shown in Table 12, and the Kaplan-Meier curves for Stage 1a Overall Survival and Stage 2 PFS are shown in Figures 1 and 2, respectively.

**Table 12 Efficacy Results from CLL11**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Stage 1 of CLL11</th>
<th>Stage 2 of CLL11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GAZYVA + Chlorambucil*</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>n = 238</td>
<td>n = 118</td>
<td>n = 333</td>
</tr>
<tr>
<td>Median Progression-Free Survival(^a)</td>
<td>27.2 months (HR 0.19 [0.14; 0.27], p-value &lt; 0.0001 stratified log-rank test)</td>
<td>11.2 months</td>
</tr>
<tr>
<td>Overall Response Rate(^b)</td>
<td>78.2%</td>
<td>33.1%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>28.2%</td>
<td>0</td>
</tr>
<tr>
<td>Complete Response with Incomplete</td>
<td>2.5%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Marrow Recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Partial Response</td>
<td>45.0%</td>
<td>30.5%</td>
</tr>
<tr>
<td>Nodular Partial Response</td>
<td>2.5%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Median Duration of Response</td>
<td>22.4 months</td>
<td>4.7 months</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
<td>HR 0.41 [0.23; 0.74]</td>
</tr>
</tbody>
</table>

*As defined by independent review. Investigator-assessed PFS was consistent with data from independent review.
Defined as best overall response rate (ORR = CR + CRi + PR + nPR).
*All Stage 1 GClb patients (n = 238) were included in the Stage 2 GClb population (n = 333).
Figure 1
Kaplan-Meier Curve of Overall Survival in Patients with CLL in CLL11 (Stage 1)

<table>
<thead>
<tr>
<th></th>
<th>Clb</th>
<th>G-Clb</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Median time (mo)</td>
<td>14.9</td>
<td>26.7</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.41</td>
<td>(0.23–0.74)</td>
</tr>
</tbody>
</table>

Figure 2
Kaplan-Meier Curve of Progression-Free Survival in Patients with CLL in CLL11 (Stage 2)

<table>
<thead>
<tr>
<th></th>
<th>R-Clb</th>
<th>G-Clb</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Median time (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.42</td>
<td>(0.33–0.54)</td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

n at risk
R-Clb  330 310 302 291 157 105 67 44 28 14 6 2 0 0
G-Clb  333 296 290 268 200 145 119 90 59 35 12 4 1 0

CI, confidence interval; PFS, progression-free survival
14.2 Follicular Lymphoma

**GADOLIN**

GADOLIN (NCT01059630) is an open-label, multicenter, randomized study including 321 patients with follicular lymphoma (FL) who had no response to or have progressed during or within 6 months of rituximab product or a rituximab product-containing regimen. These patients were randomized to receive either bendamustine alone (n = 166) or GAZYVA in combination with bendamustine (n = 155) for 6 cycles, each of 28 days duration. Patients in the GAZYVA plus bendamustine arm who did not have disease progression [patients with a complete response (CR), partial response (PR) or stable disease (SD)] at the end of the 6 cycles continued receiving GAZYVA monotherapy for 2 years. Patients were stratified according to the type of refractoriness to rituximab product (refractory to rituximab product monotherapy versus rituximab product in combination with chemotherapy) and the number of prior therapies (≤ 2 versus > 2).

GAZYVA was given by intravenous infusion as a flat dose of 1000 mg on Days 1, 8 and 15 of Cycle 1, on Day 1 of Cycles 2–6, and then every 2 months until disease progression for up to 2 years. Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (1–6) at 90 mg/m²/day when given in combination with GAZYVA or 120 mg/m²/day when given alone.

In GADOLIN, patients had a median age of 63 years, 88% were Caucasian, and 56% were male. Thirty-four percent had bulky disease (> 6 cm), 15% had at least one B-symptom at baseline and 95% had an ECOG performance status of 0–1 at baseline. The median time since initial diagnosis was 3 years and the median number of prior therapies was 2 (range 1 to 10). Forty-six percent of patients received 1 prior therapy and 33% of patients received 2 prior therapies. Twenty percent of patients were refractory to prior rituximab product monotherapy, 37% of patients were refractory to prior rituximab product plus chemotherapy induction treatment, and 41% of patients were refractory to rituximab product maintenance treatment received following rituximab product plus chemotherapy induction. Seventy-nine percent of patients were refractory to both rituximab product and an alkylating agent during any prior regimen (double refractory).

The primary objective of the study was to evaluate PFS as determined by an independent review committee (IRC). Median observation time was 21.1 months. The median PFS in the bendamustine arm was 13.8 months. Median PFS was not reached in the GAZYVA plus bendamustine arm (PFS HR = 0.48, 95% CI: 0.34-0.68; stratified log-rank test p-value < 0.0001). The investigator assessed PFS result was consistent with the IRC-assessed PFS. The median investigator-assessed PFS in the bendamustine arm was 13.7 months and the median in the GAZYVA containing arm was 29.2 months (PFS HR = 0.48, 95% CI: 0.35-0.67; stratified log-rank test p-value < 0.0001). Efficacy results are summarized in Table 13. Kaplan-Meier curves for PFS are shown in Figure 3.

An analysis conducted with 24.1 months of median observation time revealed that the median overall survival was not yet reached in either arm. Kaplan-Meier curves for OS are shown in Figure 4.
Table 13  Efficacy Results from GADOLIN\textsuperscript{a, b}

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>GAZYVA + Bendamustine followed by GAZYVA monotherapy ( n = 155 )</th>
<th>Bendamustine ( n = 166 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Progression-Free Survival (months)</td>
<td>Not Reached</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>(HR = 0.48 [0.34; 0.68], p-value &lt; 0.0001 by stratified log-rank test)</td>
<td></td>
</tr>
<tr>
<td>Best Overall Response\textsuperscript{c}</td>
<td>78.7%</td>
<td>74.7%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>15.5%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>63.2%</td>
<td>56.0%</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>Not Reached</td>
<td>11.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Based on FL population.
\textsuperscript{b} As defined by independent review.
\textsuperscript{c} Best response of CR/PR within 12 months of study start.

Figure 3

Kaplan-Meier Curve of Progression-Free Survival in Patients with FL

![Kaplan-Meier Curve](image-url)
**GALLIUM**

GALLIUM (NCT01332968) is a multicenter, open-label, randomized study including 1202 patients with previously untreated, stage II bulky, III or IV FL. Patients were randomized 1:1 to receive either GAZYVA (n = 601) or rituximab product (n = 601) in combination with chemotherapy (CHOP, CVP, or bendamustine) for 6–8 cycles. Patients were stratified by chemotherapy (selected by each site; all patients at that site received the chosen chemotherapy regimen), FLIPI (Follicular Lymphoma International Prognostic Index) risk group and geographic region. Patients with at least PR to combination therapy received monotherapy with GAZYVA (1000 mg) or rituximab product every two months until disease progression or for a maximum of two years. The study excluded patients with follicular lymphoma grade 3b or transformed disease; patients having an ANC < 1500 / μL, platelets < 75,000 / μL, or CrCl < 40 mL/min; and patients with hepatic transaminases > 2.5 x upper limit of normal unless attributable to lymphoma.

GAZYVA was given by intravenous infusion as a flat dose of 1000 mg on Days 1, 8 and 15 of cycle 1 and Day 1 of subsequent treatment cycles.

GAZYVA and bendamustine were given in six 28-day cycles. Bendamustine was administered at 90 mg/m²/day on Days 1 and 2 of each cycle, with prednisone 100 mg orally or equivalent on Day 1 of Cycle 1.

GAZYVA and CHOP were given in six 21-day cycles. Subsequently, two additional cycles of GAZYVA were given for a total of 8 GAZYVA cycles. CHOP consisted of cyclophosphamide 750 mg/m² intravenously, doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (maximum dose, 2 mg) on Day 1 and prednisone 100 mg orally on Days 1-5.

GAZYVA and CVP were given in eight 21-day cycles. CVP consisted of cyclophosphamide 750 mg/m² intravenously and vincristine 1.4 mg/m² (maximum dose, 2 mg) on Day 1 and prednisone 100 mg orally on Days 1-5.

Patients had a median age of 59 years, 81% were Caucasian, and 53% were female; 7% had Stage II, 35% had Stage III, and 56% had Stage IV disease, with 44% having bulky disease (≥ 7 cm) overall;
79% had a FLIPI score of > 2; and 97% had an ECOG performance status of 0–1. The chemotherapy was bendamustine in 57%, CHOP in 33%, and CVP in 10% of patients.

Efficacy was based on PFS per IRC, with a median observation time of 38 months. Upon interim analysis, the risk of progression or death was significantly reduced in the GAZYVA containing arm compared to the rituximab product containing arm (Table 14). Kaplan-Meier curves for PFS are shown in Figure 5. Overall response and complete remission rates were similar.

### Table 14  Efficacy in Previously Untreated Follicular Lymphoma (GALLIUM)

<table>
<thead>
<tr>
<th>Endpoint per IRC</th>
<th>GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 601</th>
<th>Rituximab product + chemotherapy followed by rituximab product monotherapy n = 601</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-Free Survival&lt;sup&gt;a&lt;/sup&gt;</td>
<td>108 (18%)</td>
<td>141 (23%)</td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>HR = 0.72 [95% CI: 0.56, 0.93], p-value = 0.0118&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate&lt;sup&gt;c&lt;/sup&gt;</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>Complete Remission Rate&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28%</td>
<td>27%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Investigator-assessed PFS was consistent with data from independent review.

<sup>b</sup> Stratified log-rank test

<sup>c</sup> After completion of combination therapy. Assessed by CT without positron emission tomography.
Figure 5
Kaplan-Meier Curves of Progression Free Survival in Patients with Previously Untreated FL

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage
GAZYVA 1000 mg/40 mL (25 mg/mL) single-dose vials containing preservative-free solution (NDC 50242-070-01) are stable at 2°C to 8°C (36°F to 46°F). Do not use beyond expiration date stamped on carton. Protect GAZYVA vials from light. DO NOT FREEZE. DO NOT SHAKE.

For the diluted product, chemical and physical stability have been demonstrated in 0.9% NaCl at concentrations of 0.4 mg/mL to 20 mg/mL for 24 hours at 2°C to 8°C (36°F to 46°F) followed by 48 hours (including infusion time) at room temperature (≤ 30°C/86°F). GAZYVA does not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. The solution for infusion should be used immediately. If not used immediately, the prepared solution may be stored up to 24 hours at 2 to 8°C. No incompatibilities between GAZYVA and polyvinyl chloride or polyolefin infusion materials have been observed in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of GAZYVA with 0.9% sodium chloride.

17 PATIENT COUNSELING INFORMATION
Advise patients to seek immediate medical attention for any of the following:

- Signs and symptoms of infusion reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, breathing problems, or chest pain [see Warnings and Precautions (5.3) and Adverse Reactions (6.1)].

- Symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy [see Warnings and Precautions (5.5) and Adverse Reactions (6.1)].
• Signs of infections including fever and cough [see Warnings and Precautions (5.6) and Adverse Reactions (6.1)].

• Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes [see Warnings and Precautions (5.1)].

• New or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems [see Warnings and Precautions (5.2)].

Advise patients of the need for:

• Periodic monitoring of blood counts [see Warnings and Precautions (5.7 and 5.8) and Adverse Reactions (6.1)].

• Avoid vaccinations with live viral vaccines [see Warnings and Precautions (5.9)].

• Patients with a history of hepatitis B infection (based on the blood test) should be monitored and sometimes treated for their hepatitis [see Warnings and Precautions (5.1)].

Advise pregnant women of potential fetal B-cell depletion [see Use in Specific Populations (8.1)].

GAZYVA® (obinutuzumab)

Manufactured by:
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A Member of the Roche Group
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U.S. License No. 1048

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