Package leaflet: Information for the patient

Gazyvaro 1,000 mg concentrate for solution for infusion
obinutuzumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Gazyvaro is and what it is used for
2. What you need to know before you are given Gazyvaro
3. How Gazyvaro is given
4. Possible side effects
5. How to store Gazyvaro
6. Content of the pack and other information

1. What Gazyvaro is and what it is used for

What Gazyvaro is

Gazyvaro contains the active substance obinutuzumab, which belongs to a group of medicines called "monoclonal antibodies". Antibodies work by attaching themselves to specific targets in your body.

What Gazyvaro is used for

Gazyvaro can be used in adults to treat two different types of cancer

- **Chronic lymphocytic leukaemia** (also called "CLL")
  - Gazyvaro is used in patients who have not had any treatment for CLL before and who have other illnesses which make it unlikely that they would be able to tolerate a full dose of a different medicine used to treat CLL called fludarabine.
  - Gazyvaro is used together with another medicine for cancer called chlorambucil.

- **Follicular lymphoma** (also called "FL")
  - Gazyvaro is used in patients who have not had any treatment for FL
  - Gazyvaro is used in patients who have had at least one treatment with a medicine called rituximab before and whose FL has come back or got worse during or after this treatment.
  - At the start of treatment for FL, Gazyvaro is used together with other medicines for cancer.
  - Gazyvaro can then be used on its own for up to 2 years as a "maintenance treatment".

How Gazyvaro works

- CLL and FL are types of cancer that affect white blood cells called "B-lymphocytes". The affected "B-lymphocytes" multiply too quickly and live too long. Gazyvaro binds to targets on the surface of the affected "B-lymphocyte" cells and causes them to die.
- When Gazyvaro is given to patients with CLL or FL together with other medicines for cancer - this slows down the time it takes for their disease to get worse.

2. What you need to know before you are given Gazyvaro

You must not be given Gazyvaro if:

- you are allergic to obinutuzumab or any of the other ingredients of this medicine (listed in section 6).

If you are not sure talk to your doctor or nurse before being given Gazyvaro.

Warnings and precautions

Talk to your doctor or nurse before you are given Gazyvaro if:
- you have an infection, or have had an infection in the past which lasted a long time or keeps coming back
- you have ever taken, or been given, medicines which affect your immune system (such as chemotherapy or immunosuppressants)
- you are taking medicines for high blood pressure or medicines used to thin your blood – your doctor might need to alter how you take these
- you have ever had heart problems
- you have ever had brain problems (such as memory problems, difficulty moving or feeling sensations in your body, eyesight problems)
- you have ever had breathing problems or lung problems
- you have ever had "hepatitis B" - a type of liver disease
- you are due to have a vaccine or you know you may need to have one in the near future.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you are given Gazyvaro.

Pay attention to the following side effects

Gazyvaro can cause some serious side effects that you need to tell your doctor or nurse about straight away. These include:

Infusion related reactions

- Tell your doctor or nurse straight away if you get any of the infusion related reactions listed at the start of section 4. Infusion related reactions can happen during the infusion or up to 24 hours after the infusion.
- If you get an infusion related reaction, you may require additional treatment, or the infusion may need to be slowed down or stopped. When these symptoms go away, or improve, the infusion can be continued. These reactions are more likely to happen with the first infusion. Your doctor may decide to stop treatment with Gazyvaro if you have a severe infusion related reaction.
- Before each infusion of Gazyvaro, you will be given medicines which help to reduce possible infusion related reactions or "tumour lysis syndrome". Tumour lysis syndrome is a potentially life-threatening complication, caused by chemical changes in the blood due to the breakdown of dying cancer cells (see section 3).

Progressive multifocal leukoencephalopathy (also called "PML")

- PML is a very rare and life-threatening brain infection that has been reported in very few patients having treatment with Gazyvaro.
- Tell your doctor or nurse straight away if you have memory loss, trouble speaking, difficulty walking or problems with your eyesight.

· If you had any of these symptoms before treatment with Gazyvaro, tell your doctor straight away if you notice any changes in them. You may need medical treatment.

Infections

· Tell your doctor or nurse straight away if you get any signs of infection after your Gazyvaro treatment (see "Infections" in section 4).

Children and adolescents

Do not give Gazyvaro to children or young people under 18 years of age. This is because there is no information about its use in these age groups.

Other medicines and Gazyvaro

Tell your doctor or nurse if you are taking, have recently taken or might start taking any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy

· Tell your doctor or nurse if you are pregnant, think you might be pregnant or are planning to have a baby. They will help you weigh up the benefit of continuing Gazyvaro against the risk to your baby.
· If you become pregnant during treatment with Gazyvaro, tell your doctor or nurse as soon as possible. This is because treatment with Gazyvaro may affect yours or the baby's health.

Breast-feeding

· Do not breast-feed during treatment with Gazyvaro or for 18 months after stopping treatment with Gazyvaro. This is because small amounts of the medicine may pass into your breast milk.

Contraception

· Use an effective method of contraception while being treated with Gazyvaro.
· Continue to use effective contraception for 18 months after stopping treatment with Gazyvaro.

Driving and using machines

Gazyvaro is not likely to affect your ability to drive, cycle or use any tools or machines. However, if you get an infusion related reaction, (see section 4), do not drive, cycle or use any tools or machines until the reaction stops.

3. How Gazyvaro is given

How Gazyvaro is given

Gazyvaro is given under the supervision of a doctor experienced in such treatment. It is given into a vein as a drip (intravenous infusion) over several hours.

The Gazyvaro treatment

Chronic lymphocytic leukaemia

· You will be given 6 treatment cycles of Gazyvaro in combination with another medicine for cancer called chlorambucil. Each cycle lasts 28 days.

- On Day 1 of your first cycle, you will be given part of your first Gazyvaro dose of 100 milligrams (mg) very slowly. Your doctor/nurse will monitor you carefully for infusion related reactions.
- If you do not have an infusion related reaction following the small part of your first dose, you may be given the rest of your first dose (900 mg) on the same day.
- If you do have an infusion related reaction following the small part of your first dose, you will be given the rest of your first dose on Day 2.

A typical schedule is shown below.
Cycle 1 - this will include three doses of Gazyvaro in the 28 days:
- Day 1 – part of your first dose (100 mg)
- Day 2 or Day 1 (continued) – remainder of first dose 900 mg
- Day 8 – full dose (1,000 mg)
- Day 15 – full dose (1,000 mg)

Cycles 2, 3, 4, 5 and 6 this will be just one dose of Gazyvaro in the 28 days:
- Day 1 – full dose (1,000 mg).

Follicular lymphoma

- You will be given 6 or 8 treatment cycles of Gazyvaro in combination with other medicines for cancer - each cycle lasts 28 or 21 days depending on which other cancer medicines are given together with Gazyvaro.
- This induction phase will be followed by a "maintenance phase" - during this time you will be given Gazyvaro every 2 months for up to 2 years as long as your disease does not progress. Based on your disease status after the initial treatment cycles your doctor will decide whether you will receive treatment in the maintenance phase.
- A typical schedule is shown below.

Induction phase

Cycle 1 - this will include three doses of Gazyvaro in the 28 or 21 days depending on which other cancer medicines are given together with Gazyvaro:
- Day 1 - full dose (1,000 mg)
- Day 8 - full dose (1,000 mg)
- Day 15 - full dose (1,000 mg).

Cycles 2-6 or 2-8 - this will be just one dose of Gazyvaro in the 28 or 21 days depending on which other cancer medicines are given together with Gazyvaro:
- Day 1 - full dose (1,000 mg).

Maintenance phase

- Full dose (1,000 mg) once every 2 months for up to 2 years as long as your disease does not progress.

Medicines given before each infusion

Before each infusion of Gazyvaro, you will be given medicines to lessen the chance of getting infusion related reactions or tumour lysis syndrome. These may include:

- fluids
- medicines to reduce a fever
- medicines to reduce pain (analgesics)
- medicines to reduce inflammation (corticosteroids)

- medicines to reduce an allergic reaction (anti-histamines)
- medicine to prevent tumour lysis syndrome (such as allopurinol).

If you miss a Gazyvaro treatment

If you miss your appointment, make another one as soon as possible. This is because for this medicine to be as effective as possible, it is important to follow the dosing schedule.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects have been reported with this medicine:

Serious side effects

Infusion related reactions

Tell your doctor or nurse straight away if you get any of the following symptoms during your infusion or up to 24 hours after having your infusion:

Most frequently reported:
- nausea
- fatigue
- dizziness
- headache
- diarrhoea
- fever, flushing or chills
- vomiting
- shortness of breath
- low or high blood pressure
- heart beating very fast
- chest discomfort

Less frequently reported:
- irregular heartbeat
- swelling of the throat or airway
- wheezing, difficulty breathing, tight chest or throat irritation

If you get any of the above, tell your doctor or nurse straight away.

Progressive multifocal leukoencephalopathy

PML is a very rare and life-threatening brain infection that has been reported with Gazyvaro.

Tell your doctor or nurse straight away if you have
- memory loss
- trouble speaking
- difficulty walking
- problems with your eyesight

If you had any of these symptoms before treatment with Gazyvaro, tell your doctor straight away if you notice any changes in them. You may need medical treatment.

Infections

You may be more likely to get an infection during and after treatment with Gazyvaro. Often these are colds, but there have been cases of more severe infections. A type of liver disease called “hepatitis B” has also been reported to reoccur in patients who have had hepatitis B in the past.

Tell your doctor or nurse straight away if you get any signs of infection during and after your Gazyvaro treatment. These include:
- fever
- cough
- chest pain
- fatigue
- painful rash
- sore throat
- burning pain when passing urine
- feeling weak or generally unwell

If you had recurring or chronic infections before the start of Gazyvaro treatment, tell your doctor about it.

Other side effects
Tell your doctor or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- fever
- lung infection
- headache
- joint pain, back pain
- feeling weak
- feeling tired
- pain in arms and legs
- diarrhoea, constipation
- sleeplessness
- hair loss, itchiness
- urinary tract infection, nose and throat inflammation, shingles
- changes in blood tests:
  - anaemia (low levels of red blood cells)
  - low levels of all types of white blood cell (combined)
  - low levels of neutrophils (a type of white blood cell)
  - low level of platelets (a type of blood cell that helps your blood to clot)
- infection of upper airways (infection of nose, pharynx, larynx and sinuses), cough

Common (may affect up to 1 in 10 people)

- cold sores
- depression, anxiety
- flu (influenza)
- weight increase
- runny or blocked nose
- eczema
- pain in mouth or throat
- muscle and bone pain in your chest
- skin cancer (squamous cell carcinoma, basal cell carcinoma)

- bone pain
- irregular heart beat (atrial fibrillation)
- problems with urinating, urinary incontinence
- high blood pressure
- problems with digestion (e.g. heartburn), haemorrhoids
- changes shown in blood tests:
  - low levels of lymphocytes (a type of white blood cells), fever associated with low levels of neutrophils (a type of white blood cells)
  - increase in potassium, phosphate or uric acid - which can cause kidney problems (part of tumour lysis syndrome)
  - decrease in potassium
- a hole in the stomach or intestines (gastrointestinal perforation, especially in cases where the cancer affects the gastrointestinal tubes)

Uncommon (may affect up to 1 in 100 people)

- abnormal coagulation, including a serious illness where clots form all over the body (disseminated intravascular coagulation)

Tell your doctor or nurse if you notice any of the side effects listed above.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

5. How to store Gazyvaro

Gazyvaro will be stored by the healthcare professionals at the hospital or clinic. The storage details are as follows:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C-8 °C). Do not freeze.
- Keep the container in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What Gazyvaro contains

- The active substance is obinutuzumab: 1,000 mg/40 mL per vial corresponding to a concentration before dilution of 25 mg/mL.

- The other ingredients are histidine, histidine hydrochloride monohydrate, trehalose dihydrate, poloxamer 188 and water for injections.

What Gazyvaro looks like and contents of the pack

Gazyvaro is a concentrate for solution for infusion and is a colourless to slightly brown liquid.
Gazyvaro is available in a pack containing 1 glass vial.

Marketing Authorisation Holder and Manufacturer

Roche Products Limited
6 Falcon Way, Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

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The following information is intended for healthcare professionals only:

Posology

Gazyvaro should be administered under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available.

Prophylaxis and premedication for tumour lysis syndrome (TLS)

Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 10^9/L) and/or renal impairment (CrCl < 70 mL/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. *allopurinol),* or suitable alternative such as a urate oxidase (e.g. *rasburicase*) starting 12-24 hours prior to start of Gazyvaro infusion as per standard practice. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed.

Prophylaxis and premedication for infusion related reactions (IRRs)

Premedication to reduce the risk of IRRs is outlined in Table 1. Corticosteroid premedication is recommended for patients with FL and mandatory for CLL patients in the first cycle (see Table 1). Premedication for subsequent infusions and other premedication should be administered as described below.

Hypotension, as a symptom of IRRs, may occur during Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration.

Table 1 Premedication to be administered before Gazyvaro infusion to reduce the risk of IRRs in CLL and FL patients

Day of treatment cycle	Patients requiring premedication	Premedication	Administration
Cycle 1: Day 1 for CLL and FL	All patients	Intravenous corticosteroid[1,4] (mandatory for CLL, recommended for FL)	Completed at least 1 hour prior to Gazyvaro infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
		Anti-histaminic medicine[3]	
Cycle 1: Day 2 for CLL only	All patients	Intravenous corticosteroid[1] (mandatory)	Completed at least 1 hour prior to Gazyvaro infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
		Anti-histaminic medicine[3]	
All subsequent infusions for CLL and FL	Patients with no IRR during the previous infusion	Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
	Patients with an IRR (Grade 1 or 2) with the previous infusion	Oral analgesic/anti-pyretic[2] Anti-histaminic medicine[3]	
	Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x 10^9/L prior to next treatment	Intravenous corticosteroid[1,4]	Completed at least 1 hour prior to Gazyvaro infusion
		Oral analgesic/anti-pyretic[2] Anti-histaminic medicine[3]	At least 30 minutes before Gazyvaro infusion

[1] *100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.*
[2] e.g. *1,000 mg acetaminophen/paracetamol*
[3] e.g. *50 mg diphenhydramine*
[4] *If a corticosteroid-containing chemotherapy regimen is administered on the same day as Gazyvaro, the corticosteroid can be administered as an oral medicinal product if given at least 60 minutes prior to Gazyvaro, in which case additional IV corticosteroid as premedication is not required.*

Dose

Chronic lymphocytic leukaemia (in combination with chlorambucil[1])

For patients with CLL the recommended dose of Gazyvaro in combination with chlorambucil is shown in Table 2.

Cycle 1

The recommended dose of Gazyvaro in combination with chlorambucil is 1,000 mg administered over Day 1 and Day 2 (or Day 1 continued), and on Day 8 and Day 15 of the first 28 day treatment cycle. Two infusion bags should be prepared for the infusion on Days 1 and 2 (100 mg for Day 1 and 900 mg for Day 2). If the first bag is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions and medical supervision are available

throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg the second bag must be administered the following day.

Cycles 2 – 6

The recommended dose of Gazyvaro in combination with chlorambucil is 1,000 mg administered on Day 1 of each cycle.

Table 2 Dose of Gazyvaro to be administered during 6 treatment cycles each of 28 days duration for patients with CLL

Cycle	Day of treatment	Dose of Gazyvaro
Cycle 1	Day 1	100 mg
	Day 2 (or Day 1 continued)	900 mg
	Day 8	1,000 mg
	Day 15	1,000 mg
Cycles 2-6	Day 1	1,000 mg

[1] Chlorambucil is given orally at 0.5 mg/kg body weight on Day 1 and Day 15 of all treatment cycles

Duration of treatment
Six treatment cycles, each of 28 day duration.

Follicular lymphoma

For patients with FL, the recommended dose of Gazyvaro in combination with chemotherapy is shown in Table 3.

Patients with previously untreated follicular lymphoma

Induction (in combination with chemotherapy[2])
Gazyvaro should be administered with chemotherapy as follows:

- Six 28-day cycles in combination with bendamustine[2] or
- Six 21-day cycles in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP), followed by 2 additional cycles of Gazyvaro alone or
- Eight 21-day cycles in combination with cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone (CVP).

Maintenance

Patients who achieve a complete or partial response to induction treatment with Gazyvaro in combination with chemotherapy should continue to receive Gazyvaro 1,000 mg as single agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first).

Patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

Induction (in combination with bendamustine[2])

Gazyvaro should be administered in six 28-day cycles in combination with bendamustine[2].

Maintenance

Patients who achieved a complete or partial response to induction treatment (i.e. the initial 6 treatment cycles) with Gazyvaro in combination with bendamustine or have stable disease should continue to receive Gazyvaro 1,000 mg as single agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first).

Table 3 Follicular lymphoma: Dose of Gazyvaro to be administered during induction treatment, followed by maintenance treatment

Cycle	Day of treatment	Dose of Gazyvaro
Cycle 1	Day 1	1,000 mg
	Day 8	1,000 mg
	Day 15	1,000 mg
Cycles 2–6 or 2-8	Day 1	1,000 mg
Maintenance	Every 2 months for 2 years or until disease progression (whichever occurs first)	1,000 mg

[2] Bendamustine is given intravenously on Days 1 and 2 of all treatment cycles (Cycles 1-6) at 90 mg/m^2/day; CHOP and CVP according to standard regimens

Duration of treatment

Induction treatment of approximately six months (six treatment cycles of Gazyvaro, each of 28 day duration when combined with bendamustine, or eight treatment cycles of Gazyvaro, each of 21 day duration when combined with CHOP or CVP) followed by maintenance once every 2 months for 2 years or until disease progression (whichever occurs first).

Method of administration

Gazyvaro is for intravenous use. It should be given as an intravenous infusion through a dedicated line after dilution. Gazyvaro infusions should not be administered as an intravenous push or bolus.

For instructions on dilution of Gazyvaro before administration, see below.
Instructions on the rate of infusion are shown in Tables 4 -6.

Chronic Lymphocytic Leukaemia

Table 4 Chronic lymphocytic leukaemia: Standard infusion rate in the absence of IRRs/hypersensitivity and recommendations in case an IRR occurred with previous infusion

<table>
<tr><th>Cycle</th><th>Day of treatment</th><th>Rate of infusion
The infusion rate may be escalated provided that the patient can tolerate it. For management IRRs that occur during the infusion, refer to “Management of IRRs”.</th></tr>
<tr><td rowspan="4">Cycle 1</td><td>Day 1
(100 mg)</td><td>Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.</td></tr>
<tr><td>Day 2
(or Day 1 continued)
(900 mg)</td><td>If no IRR 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.

If the patient experienced an IRR during the previous infusion, start with administration at 25 mg/hr. The rate of infusion can be escalated in increments up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.</td></tr>
<tr><td>Day 8
(1,000 mg)</td><td rowspan="3">If no IRR occurred during the previous infusion when the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

If the patient experienced an IRR during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50mg/hr every 30 minutes to a maximum rate of 400 mg/hr.</td></tr>
<tr><td>Day 15
(1,000 mg)</td></tr>
<tr><td>Cycles 2-6</td><td>Day 1
(1,000 mg)</td></tr>
</table>

Follicular lymphoma (FL)

Gazyvaro should be administered at the standard infusion rate in Cycle 1 (see Table 5). In patients who do not experience Grade ≥3 infusion related reactions (IRRs) during Cycle 1, Gazyvaro may be administered as a short (approximately 90 minute) duration infusion (SDI) from Cycle 2 onwards (see Table 6).

Table 5 Follicular lymphoma: Standard infusion rate and recommendations in case an IRR occurred with previous infusion

<table>
<tr><th>Cycle</th><th>Day of treatment</th><th>Rate of infusion
The infusion rate may be escalated provided that the patient can tolerate it. For management of IRRs that occur during the infusion, refer to “Management of IRRs”.</th></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1
(1,000 mg)</td><td>Administer at 50 mg/hr. The rate of 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
(1,000 mg)</td><td rowspan="3">If no IRR or if an IRR Grade 1 occurred during the previous infusion when the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

If the patient experienced an IRR of Grade 2 or higher during the previous infusion administer at 50 mg/hr. The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.</td></tr>
<tr><td>Day 15
(1,000 mg)</td></tr>
<tr><td>Cycles 2–6 or 2–8</td><td>Day 1
(1,000 mg)</td></tr>
<tr><td>Maintenance</td><td>Every 2 months for 2 years or until disease progression (whichever occurs first)</td><td></td></tr>
</table>

Table 6 Follicular lymphoma: Short duration infusion rate and recommendations in case an IRR occurred with previous infusion

<table>
<tr><th>Cycle</th><th>Day of treatment</th><th>Rate of infusion
For management of IRRs that occur during the infusion, refer to “Management of IRRs”.</th></tr>
<tr><td>Cycles 2–6 or 2–8</td><td>Day 1
(1,000 mg)</td><td rowspan="2">If no IRR of Grade ≥3 occurred during Cycle 1:
100 mg/hr for 30 minutes, then 900 mg/hr for approximately 60 minutes.

If an IRR of Grade 1-2 with ongoing symptoms or a Grade 3 IRR occurred during the previous SDI infusion, administer the next obinutuzumab at the standard infusion rate (see Table 5).</td></tr>
<tr><td>Maintenance</td><td>Every 2 months for 2 years or until disease progression (whichever occurs first)</td></tr>
</table>

Management of IRRs (all indications)

Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations of Gazyvaro as outlined below.

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 4 - 6). For CLL patients receiving the Day 1 (Cycle 1) dose split over two days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.
  The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.
- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 4 -6). For CLL patients receiving the Day 1 (Cycle 1) dose split over two days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

Management of IRRs occurring during SDI

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and not greater than 400 mg/hr.

If the patient experiences a second Grade 3 IRR after resuming the infusion, the infusion must be stopped and therapy must be permanently discontinued. If the patient is able to complete the infusion without further Grade 3 IRRs, the next infusion should be given at a rate not higher than the standard rate.

- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 5- 6).

<u>Instructions for dilution</u>

Gazyvaro should be prepared by a healthcare professional using aseptic technique. Do not shake the vial. Use a sterile needle and syringe to prepare Gazyvaro.

For CLL cycles 2 – 6 and all FL cycles

Withdraw 40 mL of concentrate from the vial and dilute in polyvinyl chloride (PVC) or non-PVC polyolefin infusion bags containing sodium chloride 9 mg/mL (0.9%) solution for injection.

CLL only – Cycle 1

To ensure differentiation of the two infusion bags for the initial 1,000 mg dose, it is recommended to utilise bags of different sizes to distinguish between the 100 mg dose for Cycle 1 Day 1 and the 900 mg dose for Cycle 1 Day 1 (continued) or Day 2. To prepare the 2 infusion bags, withdraw 40 mL of concentrate from the vial and dilute 4 mL into a 100 mL PVC or non-PVC polyolefin infusion bag

and the remaining 36 mL in a 250 mL PVC or non-PVC polyolefin infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection. Clearly label each infusion bag.

Dose of Gazyvaro to be administered	Required amount of Gazyvaro concentrate	Size of PVC or non-PVC polyolefin infusion bag
100 mg	4 mL	100 mL
900 mg	36 mL	250 mL
1,000 mg	40 mL	250 mL

No incompatibilities have been observed between Gazyvaro, in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of Gazyvaro with sodium chloride 9 mg/mL (0.9%) solution for injection, and:

- PVC, polyethylene (PE), polypropylene or polyolefin bags
- PVC, polyurethane (PUR) or PE infusion sets
- optional inline filters with product contact surfaces of polyethersulfone (PES), a 3-way stopcock infusion aid made from polycarbonate (PC), and catheters made from polyetherurethane (PEU).

Do not use other diluents such as glucose (5%) solution.

The bag should be gently inverted to mix the solution in order to avoid excessive foaming. The diluted solution should not be shaken or frozen.

Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration.

After dilution, chemical and physical stability have been demonstrated in sodium chloride 9 mg/mL (0.9%) solution for injection at concentrations of 0.4 mg/mL to 20 mg/mL for 24 hours at 2°C to 8°C followed by 48 hours (including infusion time) at ≤ 30°C.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.