ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Gazyvaro 1,000 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 40 mL concentrate contains 1,000 mg obinutuzumab, corresponding to a concentration before dilution of 25 mg/mL.

Obinutuzumab is a Type II humanised anti-CD20 monoclonal antibody of the IgG1 subclass derived by humanisation of the parental B-Ly1 mouse antibody and produced in the Chinese Hamster Ovary cell line by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly brownish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy (see section 5.1).

4.2 Posology and method of administration

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

Posology

Prophylaxis for tumour lysis syndrome (TLS)
Prophylaxis with adequate hydration and administration of uricostatics (e.g. *allopurinol*) starting 12-24 hours prior to start of therapy is recommended for patients with high circulating lymphocyte count (> 25 x 10^9/L) to reduce the risk of tumour lysis syndrome (see section 4.4).

Prophylaxis and premedication for infusion related reactions (IRRs)
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 (see section 4.4).

Table 1 Premedication to be administered before Gazyvaro infusion to reduce the risk of infusion related reactions (see section 4.4)

Day of treatment cycle	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1: Day 1	All patients	Intravenous corticosteroid[1]	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	All patients	Intravenous corticosteroid[1]	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 8, Day 15	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]	Completed at least 1 hour prior to Gazyvaro infusion
Cycles 2-6: Day 1	All patients	Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
	Patients with an IRR (Grade 1 or more) with the previous infusion	Anti-histaminic medicine[3]	

[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*

Dose
The recommended dose of Gazyvaro is shown in Table 2.

Cycle 1
The recommended dose of Gazyvaro is 1,000 mg administered over Day 1 and Day 2, 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 to 6
The recommended dose of Gazyvaro is 1,000 mg administered on Day 1.

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

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

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

Delayed or missed doses
If a planned dose of Gazyvaro is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for Gazyvaro should be maintained between doses.

Dose modifications during treatment
No dose reductions of Gazyvaro are recommended.

Special populations

Elderly
No dose adjustment is required in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance [CrCl] 30-89 mL/min) (see section 5.2). The safety and efficacy of Gazyvaro has not been established in patients with severe renal impairment (CrCl < 30 mL/min).

Hepatic impairment
The safety and efficacy of Gazyvaro in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.

Paediatric population
The safety and efficacy of Gazyvaro in children and adolescents aged below 18 years has not been established. No data are available.

Method of administration

Gazyvaro is for intravenous use. It should be given as an intravenous infusion through a dedicated line after dilution (see section 6.6). Gazyvaro infusions should not be administered as an intravenous push or bolus.

For instructions on dilution of Gazyvaro before administration, see section 6.6.

Instructions on the rate of infusion are shown in Table 3.

Table 3 Standard infusion rate in the absence of infusion reactions/hypersensitivity

Cycle	Day of treatment	Rate of infusion
Cycle 1	Day 1 (100 mg)	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2 (or Day 1 continued) (900 mg)	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.
	Day 8	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.
	Day 15	
Cycles 2-6	Day 1	

Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations of Gazyvaro as outlined below (see also section 4.4).

- 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 Table 3). The Day 1 (Cycle 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 Table 3). The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file.

Infusion Related Reactions (IRRs)

The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyvaro were IRRs, which occurred predominantly during infusion of the first 1,000 mg. In patients who received the combined measures for prevention of IRRs (adequate glucocorticoid, oral analgesic/anti-histamine, omission of antihypertensive medicine in the morning of the first infusion, and the Cycle 1 Day 1 dose administered over 2 days) as described in section 4.2, a decreased incidence of all Grade IRRs was observed. The rates of Grade 3-4 IRRs (which were based on a relatively small number of patients) were similar before and after mitigation measures were implemented. Mitigation measures to reduce IRRs should be followed (see section 4.2). The incidence and severity of infusion-related symptoms decreased substantially after the first 1,000 mg was infused, with most patients having no IRRs during subsequent administrations of Gazyvaro (see section 4.8).

In the majority of patients, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from immunoglobulin E (IgE) mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumour burden (i.e. high peripheral lymphocyte count in CLL [> 25 x 10^9/L] may be at increased risk of severe IRRs. Patients with renal impairment (CrCl < 50 mL/min) and patients with both Cumulative Illness Rating Scale (CIRS) > 6 and CrCl < 70 mL/min are more at risk of IRRs, including severe IRRs (see section 4.8).

Cases of cytokine release syndrome have also been reported with Gazyvaro. For information on prophylaxis see section 4.2.

If the patient experiences an IRR, the infusion should be managed according to the grade of the reaction. For Grade 4 IRRs, the infusion must be stopped and therapy permanently discontinued. For Grade 3 IRRs, the infusion must be temporarily interrupted and appropriate medicine administered to treat the symptoms. For Grade 1-2 IRRs, the infusion must be slowed down and symptoms treated as appropriate. Upon resolution of symptoms, the infusion can be restarted, except following Grade 4 IRRs, at no more than half the previous rate and, if the patient does not experience the same adverse event with the same severity, the infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If the previous infusion rate was not well tolerated, instructions for the Cycle 1, Day 1 and Day 2 infusion rate should be used (see Table 3 in section 4.2).

Patients must not receive further Gazyvaro infusions if they experience:
- acute life-threatening respiratory symptoms,
- a Grade 4 (i.e. life threatening) IRR or,
- a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion).

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension 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. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.

Hypersensitivity reactions including anaphylaxis

Anaphylaxis has been reported in patients treated with Gazyvaro. Hypersensitivity may be difficult to distinguish from IRRs. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion must be stopped and treatment permanently discontinued. Patients with known IgE mediated hypersensitivity to obinutuzumab must not be treated (see section 4.3).

Tumour lysis syndrome (TLS)

Tumour lysis syndrome (TLS) has been reported with Gazyvaro. Patients who are considered to be at risk of TLS (e.g. patients with a high tumour burden or a high circulating lymphocyte count [> 25 x 10^9/L]) should receive adequate tumour lysis prophylaxis with uricostatics (e.g. allopurinol) and hydration starting 12-24 hours prior to the infusion of Gazyvaro (see section 4.2). For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Neutropenia

Severe and life-threatening neutropenia including febrile neutropenia has been reported during treatment with Gazyvaro. Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. If treatment is necessary it should be administered in

accordance with local guidelines and the administration of granulocyte-colony stimulating factors should be considered. Any signs of concomitant infection should be treated as appropriate. Dose delays should be considered in case of severe or life-threatening neutropenia. It is strongly recommended that patients with severe and long lasting (>1 week) neutropenia receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered. Cases of late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia (see section 4.8).

Thrombocytopenia

Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with Gazyvaro. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of thrombocytopenia (see section 4.8). Fatal haemorrhagic events have also been reported in Cycle 1 in patients treated with Gazyvaro. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies which could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

Worsening of pre-existing cardiac conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyvaro (see section 4.8). These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

Infections

Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro in patients with a history of recurring or chronic infections. Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Gazyvaro therapy. Fatal infections have been reported. Patients with both CIRS > 6 and CrCl < 70 mL/min are more at risk of infections, including severe infections (see section 4.8).

Hepatitis B reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including Gazyvaro (see section 4.8). Hepatitis B virus screening should be performed in all patients before initiation of treatment with Gazyvaro. At a minimum this should include hepatitis B surface antigen (HBsAg) status and hepatitis B core antibody (HBcAb) status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with Gazyvaro. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation.

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with Gazyvaro (see section 4.8). The diagnosis of PML should be considered in any patient presenting with

new-onset or changes to pre-existing neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as "cortical" (e.g. aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (cerebrospinal fluid testing for John Cunningham viral DNA). Therapy with Gazyvaro should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Immunisation

The safety of immunisation with live or attenuated viral vaccines following Gazyvaro therapy has not been studied and vaccination with live virus vaccines is not recommended during treatment and until B cell recovery.

Exposure in utero to obinutuzumab and vaccination of newborns with live virus vaccines

Due to the potential depletion of B cells in newborns following exposure to obinutuzumab during pregnancy, newborns should be monitored for B cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B cell count has recovered (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Pharmacokinetic interactions

Obinutuzumab is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP450), uridine diphosphate glucuronyltransferase (UGT) enzymes and transporters such as P-glycoprotein. Therefore, no pharmacokinetic interaction is expected with drugs known to be metabolised by these enzyme systems.

Pharmacodynamic interactions

Vaccination with live virus vaccines is not recommended during treatment and until B cell recovery because of the immunosuppressive effect of obinutuzumab (see section 4.4).

The combination of obinutuzumab with chlorambucil may increase neutropenia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during and for 18 months after treatment with Gazyvaro.

Pregnancy

A reproduction study in cynomolgus monkeys showed no evidence of embryofoetal toxicity or teratogenic effects but resulted in a complete depletion of B lymphocytes in offspring. B cell counts returned to normal levels in the offspring, and immunologic function was restored within 6 months of birth. Furthermore, the serum concentrations of obinutuzumab in offspring were similar to those in the mothers on day 28 post-partum, suggesting that obinutuzumab crosses the placenta (see section 5.3).

There are no data from the use of obinutuzumab in pregnant women. Gazyvaro should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

In case of exposure during pregnancy, depletion of B cells may be expected in newborns due to the pharmacological properties of the product. Consequently, newborns should be monitored for B cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B cell count has recovered (see section 4.4).

Breast-feeding

Animal studies have shown excretion of obinutuzumab in breast milk (see section 5.3).

Because human immunoglobulin G (IgG) is excreted in human milk and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue breast-feeding during Gazyvaro therapy and for 18 months after the last dose of Gazyvaro.

Fertility

No specific studies in animals have been performed to evaluate the effect of obinutuzumab on fertility. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies in cynomolgus monkeys (see section 5.3).

4.7 Effects on ability to drive and use machines

Gazyvaro has no or negligible influence on the ability to drive and use machines. IRRs are very common during the first infusion of Gazyvaro, and patients experiencing infusion related symptoms should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The adverse drug reactions (ADRs) described in this section were identified during treatment and follow up in the pivotal clinical study, BO21004/CLL11, in which Gazyvaro was given in combination with chlorambucil vs chlorambucil alone (Stage 1) or rituximab plus chlorambucil (Stage 2). In patients treated with Gazyvaro in combination with chlorambucil, 81% of patients received all 6 treatment cycles compared to 89% of patients in the rituximab plus chlorambucil arm and 67% of patients in the chlorambucil alone arm.

The most frequently observed ADRs in patients receiving Gazyvaro were IRRs, which occurred in the majority of patients during the first cycle (see section 4.4). The incidence of infusion-related symptoms decreased substantially from 65% with the infusion of the first 1,000 mg of Gazyvaro to less than 3% with subsequent infusions.

Neutropenia and thrombocytopenia occurred in 41% and 15% of patients, respectively, in the pivotal study, with the incidence of Grade 3-5 infection being 16% in the Gazyvaro plus chlorambucil arm (see section 4.4).

Other serious ADRs reported during clinical development include tumour lysis syndrome, cardiac events and, very rarely, PML (see section 4.4).

Table 4 summarises the ADRs that occurred at a higher incidence (difference of ≥2%) in patients receiving Gazyvaro plus chlorambucil as compared to chlorambucil alone or rituximab plus chlorambucil.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Table 4 Summary of ADRs reported with a higher incidence (difference of ≥2%) in patients receiving Gazyvaro plus chlorambucil as compared to chlorambucil alone or rituximab plus chlorambucil (Study BO21004/CLL11)*

Frequency	All Grades % Gazyvaro + chlorambucil	Grades 3-5† % Gazyvaro + chlorambucil
Infections and infestations		
Common	Urinary tract infection, nasopharyngitis, oral herpes, rhinitis‡, pharyngitis	Urinary tract infection
Uncommon		Nasopharyngitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Common	Squamous cell carcinoma of skin	Squamous cell carcinoma of skin
Blood and lymphatic system disorders		
Very common	Neutropenia, thrombocytopenia, anaemia	Neutropenia, thrombocytopenia
Common	Leukopenia	Anaemia, leukopenia
Metabolism and nutrition disorders		
Common	Tumour lysis syndrome, hyperuricaemia	Tumour lysis syndrome
Uncommon		Hyperuricaemia
Cardiac disorders		
Common	Atrial fibrillation	
Uncommon		Atrial fibrillation
Vascular disorders		
Common	Hypertension	Hypertension
Respiratory, thoracic and mediastinal disorders		
Common	Cough	
Gastrointestinal disorders		
Very common	Diarrhoea	
Common	Constipation	Diarrhoea
Skin and subcutaneous tissue disorders		
Common	Alopecia	
Musculoskeletal and connective tissue disorders		
Common	Arthralgia, back pain, musculoskeletal chest pain	
Uncommon		Arthralgia, back pain, musculoskeletal chest pain
General disorders and administration site conditions		
Very common	Pyrexia	
Uncommon		Pyrexia
Investigations		
Common	White blood cell count decreased‡, neutrophil count decreased, weight increased	White blood cell count decreased‡, neutrophil count decreased
Injury, poisoning and procedural complications		
Very common	Infusion related reactions	Infusion related reactions

* In all Grades or Grade 3-5.

† No Grade 5 adverse reactions have been observed with a difference of ≥ 2% between the treatment arms

‡ While this event was reported with a difference of ≥2% between the treatment arms in Stage 1 of the study, it was no longer reported with a difference of ≥2% between the treatment arms with the Stage 1 update and the Stage 2 data.

Description of selected adverse reactions

Infusion-related reactions (IRRs)
The incidence of IRRs was higher in the Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm. The incidence of IRRs was 65% with the infusion of the first 1,000 mg of Gazyvaro (20% of patients experiencing a Grade 3-5 IRR, with no fatal events reported). Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyvaro. The incidence of IRRs with subsequent infusions was 3% with the second 1,000 mg dose and 1% thereafter. No Grade 3-5 IRRs were reported beyond the first 1,000 mg infusions of Cycle 1.

Most frequently reported symptoms associated with an IRR were nausea, chills, hypotension, pyrexia, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia, and diarrhoea. Respiratory and cardiac symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and atrial fibrillation have also been reported (see section 4.4).

Neutropenia and infections
The incidence of neutropenia was higher in the Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm with the neutropenia resolving spontaneously or with use of granulocyte-colony stimulating factors. The incidence of infection was 38% in the Gazyvaro plus chlorambucil arm and 37% in the rituximab plus chlorambucil arm (with Grade 3-5 events reported in 12% and 14%, respectively and fatal events reported in < 1% in both treatment arms). Cases of prolonged neutropenia (2% in the Gazyvaro plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the Gazyvaro plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported (see section 4.4).

Thrombocytopenia
The incidence of thrombocytopenia was higher in the Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm especially during the first cycle. Four percent of patients treated with Gazyvaro plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the Gazyvaro infusion) (see section 4.4). The overall incidence of haemorrhagic events was similar in the Gazyvaro treated arm and in the rituximab treated arm. The number of fatal haemorrhagic events was balanced between the treatment arms; however, all of the events in patients treated with Gazyvaro were reported in Cycle 1. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Special populations

Elderly
In the pivotal study, 46% (156 out of 336) of patients with CLL treated with Gazyvaro plus chlorambucil were 75 years old or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than those patients < 75 years of age.

Renal impairment
In the pivotal study, 27% (90 out of 336) of patients with CLL treated with Gazyvaro plus chlorambucil had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than those with CrCl ≥50 mL/min.

Additional safety information from clinical studies experience

Progressive multifocal leukoencephalopathy (PML)
PML has been reported in patients treated with Gazyvaro (see section 4.4).

Hepatitis B reactivation
Cases of hepatitis B reactivation have been reported in patients treated with Gazyvaro (see section 4.4).

Worsening of pre-existing cardiac conditions
Cases of arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyvaro (see section 4.4). These events may occur as part of an IRR and can be fatal.

Laboratory abnormalities
Transient elevation in liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase) has been observed shortly after the first infusion of Gazyvaro.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No experience with overdose is available from human clinical studies. In clinical studies with Gazyvaro, doses ranging from 50 mg up to and including 2,000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose dependent.

Patients who experience overdose should have immediate interruption or reduction of their infusion and be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell depleted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC15

Mechanism of action

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of obinutuzumab results in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, macrophages and monocytes as compared to non-glycoengineered antibodies.

In nonclinical studies, obinutuzumab induces direct cell death and mediates antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells. In addition, *in vivo*, obinutuzumab mediates a low degree of complement dependent cytotoxicity (CDC). Compared to Type I antibodies, obinutuzumab, a Type II antibody, is characterised by an enhanced direct cell death induction with a concomitant reduction in CDC at an equivalent dose. Obinutuzumab, as a glycoengineered antibody, is characterised by enhanced antibody-dependent cellular cytotoxicity (ADCC) compared to non-glycoengineered antibodies at an equivalent dose. In animal models obinutuzumab mediates potent B-cell depletion and antitumour efficacy.

In the pivotal clinical study BO21004/CLL11, 91% (40 out of 44) of evaluable patients treated with Gazyvaro were B-cell depleted (defined as CD19+ B cell counts < 0.07 x 10^9/L) at the end of

treatment period and remained depleted during the first 6 months of follow up. Recovery of B-cells was observed within 12-18 months of follow up in 35% (14 out of 40) of patients without progressive disease and 13% (5 out of 40) with progressive disease.

Clinical efficacy and safety

A Phase III international, multicentre, open label, randomised, two-stage, three-arm clinical study (BO21004/CLL11) investigating the efficacy and safety of Gazyvaro plus chlorambucil (GClb) compared to rituximab plus chlorambucil (RClb) or chlorambucil (Clb) alone was conducted in patients with previously untreated chronic lymphocytic leukaemia with comorbidities.

Prior to enrolment, patients had to have documented CD20+ CLL, and one or both of the following measures of coexisting medical conditions: comorbidity score (CIRS) of greater than 6 or reduced renal function as measured by CrCl <70 mL/min. Patients with inadequate liver function (National Cancer Institute – Common Terminology Criteria for Adverse Events Grade 3 liver function tests (AST, ALT > 5 x ULN for > 2 weeks; bilirubin > 3 x ULN) and renal function (CrCl < 30 mL/min) were excluded. Patients with one or more individual organ/system impairment score of 4 as assessed by the CIRS definition, excluding eyes, ears, nose, throat and larynx organ system, were excluded.

A total of 781 patients were randomized 2:2:1 to receive Gazyvaro plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1a compared Gazyvaro plus chlorambucil to chlorambucil alone in 356 patients and Stage 2 compared Gazyvaro plus chlorambucil to rituximab plus chlorambucil in 663 patients. Efficacy results are summarized in Table 5 and in Figures 1-3.

In the majority of patients, Gazyvaro was given intravenously as a 1,000 mg initial dose administered on Day 1, Day 8 and Day 15 of the first treatment cycle. In order to reduce the rate of infusion reactions in patients, an amendment was implemented and 140 patients received the first Gazyvaro dose administered over 2 days (Day 1 [100 mg] and Day 2 [900 mg]) (see section 4.2 and 4.4). For each subsequent treatment cycle (Cycles 2 to 6), patients received Gazyvaro 1,000 mg on Day 1 only. Chlorambucil was given orally at 0.5 mg/kg body weight on Day 1 and Day 15 of all treatment cycles (1 to 6).

The demographics data and baseline characteristics were well balanced between the treatment groups. The majority of patients were Caucasian (95%) and male (61%). The median age was 73 years, with 44% being 75 years or older. At baseline, 22% of patients had Binet Stage A, 42% had Binet Stage B and 36% had Binet Stage C.

The median comorbidity score was 8 and 76% of the patients enrolled had a comorbidity score above 6. The median estimated CrCl was 62 mL/min and 66% of all patients had a CrCl < 70 mL/min. Forty-two percent of patients enrolled had both a CrCl < 70 mL/min and a comorbidity score of > 6. Thirty-four percent of patients were enrolled on comorbidity score alone, and 23% of patients were enrolled with only impaired renal function.

The most frequently reported coexisting medical conditions (using a cut off of 30% or higher), in the MedDRA body systems are: Vascular disorders (73%), Cardiac disorders (46%), Gastrointestinal disorders (38%), Metabolism and nutrition disorders (40%), Renal and urinary disorders (38%), Musculoskeletal and connective tissue disorders (33%).

Table 5 Summary of efficacy from BO21004/CLL11 study

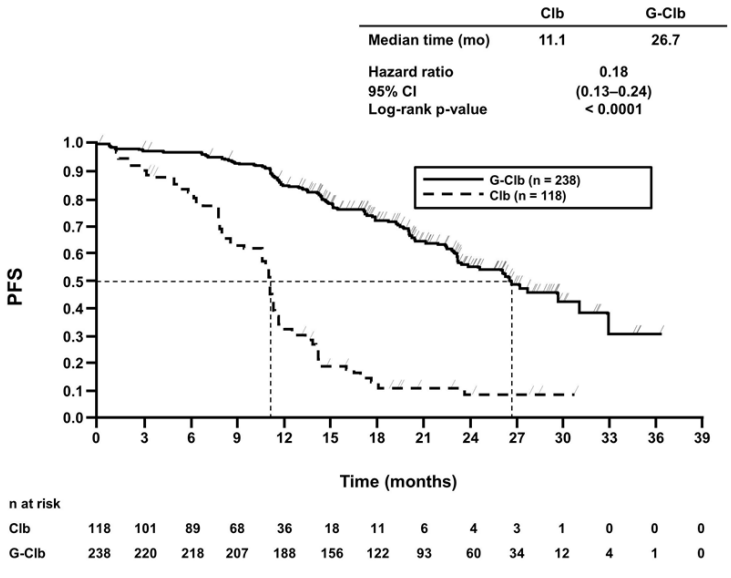
	Stage 1a		Stage 2	
	Chlorambucil N=118	**Gazyvaro + chlorambucil N= 238**	**Rituximab + chlorambucil N= 330**	**Gazyvaro + chlorambucil N= 333**
	22.8 months median observation time		**18.7 months median observation time**	
Primary endpoint				
Investigator-assessed PFS (PFS-INV)[a]				
Number (%) of patients with event	96 (81.4%)	93 (39.1%)	199 (60.3%)	104 (31.2%)
Median duration of PFS (months)	11.1	26.7	15.2	26.7
Hazard ratio (95% CI)	0.18 [0.13; 0.24]		0.39 [0.31; 0.49]	
p-value (Log-Rank test, stratified[b])	<0.0001		<0.0001	
Key secondary endpoints				
IRC-assessed PFS (PFS-IRC)[a]				
Number (%) of patients with event	90 (76.3%)	89 (37.4%)	183 (55.5%)	103 (30.9%)
Median duration of PFS (months)	11.2	27.2	14.9	26.7
Hazard ratio (95% CI)	0.19 [0.14; 0.27]		0.42 [0.33; 0.54]	
p-value (Log-Rank test, stratified[b])	<0.0001		<0.0001	
End of treatment response rate				
No. of patients included in the analysis	118	238	329	333
Responders (%)	37 (31.4%)	184 (77.3%)	214 (65.0%)	261 (78.4%)
Non-responders (%)	81 (68.6%)	54 (22.7%)	115 (35.0%)	72 (21.6%)
Difference in response rate, (95% CI)	45.95 [35.6; 56.3]		13.33 [6.4; 20.3]	
p-value (Chi-squared Test)	<0.0001		0.0001	
No. of complete responders[c] (%)	0 (0.0%)	53 (22.3%)	23 (7.0%)	69 (20.7%)
Molecular remission at end of treatment[d]				
No. of patients included in the analysis	90	168	244	239
MRD negative[e] (%)	0 (0%)	45 (26.8%)	6 (2.5%)	61 (25.5%)
MRD positive[f] (%)	90 (100%)	123 (73.2%)	238 (97.5%)	178 (74.5%)
Difference in MRD rates, (95% CI)	26.79 [19.5; 34.1]		23.06 [17.0; 29.1]	
Event free survival				
No. (%) of patients with event	103 (87.3%)	104 (43.7%)	208 (63.0 %)	118 (35.4 %)
Median time to event (months)	10.8	26.1	14.3	26.1
Hazard ratio (95% CI)	0.19 [0.14; 0.25]		0.43 [0.34; 0.54]	
p-value (Log-Rank test, stratified[b])	<0.0001		<0.0001	
Time to new anti-leukemic therapy				
No. (%) of patients with event	65 (55.1%)	51 (21.4%)	86 (26.1%)	55 (16.5%)
Median duration of event (months)	14.8	-	30.8	-
Hazard ratio (95% CI)	0.24 [0.16; 0.35]		0.59 [0.42; 0.82]	
p-value (Log-Rank test, stratified[b])	<0.0001		<0.0018	

	Stage 1a		Stage 2	
	Chlorambucil N=118	**Gazyvaro + chlorambucil N= 238**	**Rituximab + chlorambucil N= 330**	**Gazyvaro + chlorambucil N= 333**
	22.8 months median observation time		**18.7 months median observation time**	
Overall survival				
No. (%) of patients with event	24 (20.3%)	22 (9.2%)	41 (12.4%)	28 (8.4%)
Median time to event (months)	NR	NR	NR**	NR**
Hazard ratio (95% CI)	0.41 [0.23; 0.74]		0.66 [0.41; 1.06] **	
p-value (Log-Rank test, stratified[b])	0.0022		0.0849**	

PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, MRD: Minimal Residual Disease
[a] Defined as the time from randomization to the first occurrence of progression, relapse or death from any cause as assessed by the investigator
[b] stratified by Binet stage at baseline
[c] Includes 11 patients in the GClb arm with a complete response with incomplete marrow recovery
[d] Blood and bone marrow combined
[e] MRD negativity is defined as a result below 0.0001
[f] Includes MRD positive patients and patients who progressed or died before the end of treatment
NR = Not reached
** Data not yet mature

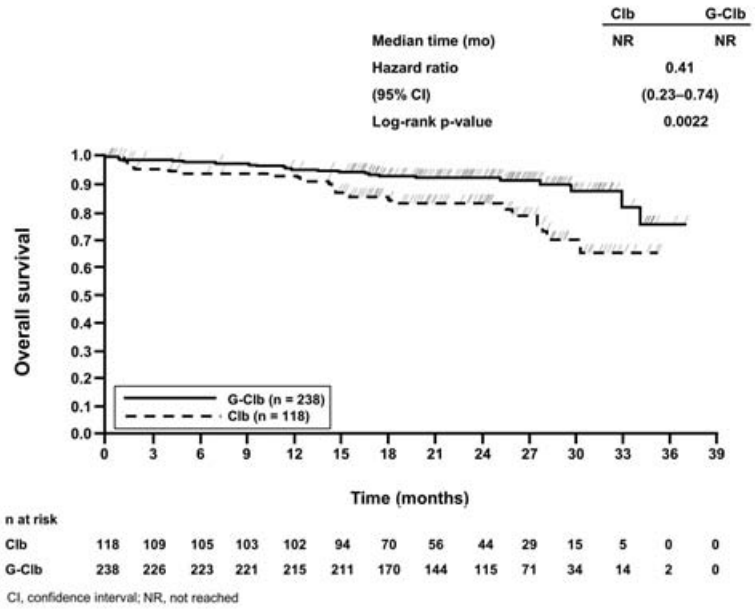
Overall survival for Stage 1a is presented in Figure 2. Overall survival for Stage 2 will continue to be followed and is not yet mature. Results of the PFS subgroup analysis (i.e. sex, age, Binet stages, CrCl, CIRS score, beta2-microglobulin, IGVH status, chromosomal abnormalities, lymphocyte count at baseline) were consistent with the results seen in the overall Intent-to-Treat population. The risk of disease progression or death was reduced in the GClb arm compared to the RClb arm and Clb arm in all subgroups except in the subgroup of patients with deletion 17p. In the small subgroup of patients with deletion 17p, only a positive trend was observed compared to Clb (HR=0.42, p=0.0892); no benefit was observed compared to RClb. For subgroups, reduction of the risk of disease progression or death ranged from 92% to 58% for GClb versus Clb and 72% to 29% for GClb versus RClb.

Figure 1 Kaplan-Meier curve of Investigator assessed progression-free survival from Stage 1a



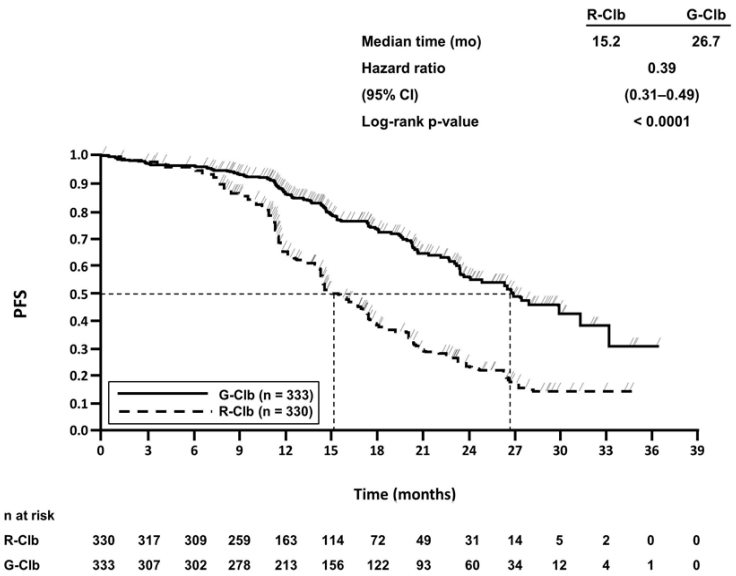
CI, confidence interval; PFS, progression-free survival

Figure 2 Kaplan-Meier curve of overall survival from Stage 1a



CI, confidence interval; NR, not reached

Figure 3 Kaplan-Meier curve of investigator assessed progression-free survival from Stage 2



CI, confidence interval; PFS, progression-free survival

Quality of life

In the QLQC30 and QLQ-CLL-16 questionnaires conducted during the treatment period, no substantial difference in any of the subscales was observed. Data during follow up, especially for the chlorambucil alone arm, is limited. However, no notable differences in quality of life during follow up have been identified to date.

Health-related quality of life assessments, specific to fatigue through treatment period, show no statistically significant difference suggesting that the addition of Gazyvaro to a chlorambucil regimen does not increase the experience of fatigue for patients.

Immunogenicity
Patients in the pivotal study BO21004/CLL11 were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Gazyvaro. In patients treated with Gazyvaro 8 out of 140 patients in the randomised phase and 2 out of 6 in the run in phase tested positive for ATA at 12 months of follow up. Of these patients, none experienced anaphylactic or hypersensitivity reactions that were considered related to ATA, nor was clinical response affected.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, assay robustness to quantities of Gazyvaro in the circulation, sample handling, timing of sample collection, concomitant medicines and underlying disease. For these reasons, comparison of incidence of antibodies to Gazyvaro with the incidence of antibodies to other products may be misleading.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Gazyvaro in all subsets of the paediatric population in Chronic Lymphocytic Leukaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

A population pharmacokinetic (PK) model was developed to analyse the PK data in 678 non-Hodgkin's lymphoma (NHL) and CLL patients from Phase I, Phase II and Phase III studies who received obinutuzumab. This population PK model was used to describe the PK characteristics of obinutuzumab in patients with CLL.

Absorption

Obinutuzumab is administered intravenously, therefore absorption is not applicable. There have been no studies performed with other routes of administration. From the population PK model, after the Cycle 6 Day 1 infusion in CLL patients, the estimated median C_{max} value was 473.2 μg/mL and AUC(τ) value was 9516 μg•d/mL.

Distribution

Following intravenous administration, the volume of distribution of the central compartment (2.76 L), approximates serum volume, which indicates distribution is largely restricted to plasma and interstitial fluid.

Biotransformation

The metabolism of obinutuzumab has not been directly studied. Antibodies are mostly cleared by catabolism.

Elimination

The clearance of obinutuzumab on Cycle 6 in CLL patients is approximately 0.083 L/day with a median elimination t½ of 30.3 days. Obinutuzumab elimination comprises a time varying clearance model with two parallel pathways which describe clearance, a linear clearance pathway and a non-linear clearance pathway which changes as a function of time. During the initiation of treatment, the non-linear time-varying clearance pathway is dominant and accounts for the major clearance pathway. As treatment progresses, the impact of this pathway diminishes and the linear clearance pathway predominates. This is indicative of target mediated drug disposition (TMDD), where the initial abundance of CD20 cells causes a rapid depletion of obinutuzumab. However, once the majority of CD20 cells are bound to obinutuzumab, there is reduced impact of TMDD on PK.

Pharmacokinetic/pharmacodynamic relationship(s)

In the population pharmacokinetic analysis, gender was found to be a covariate which explains some of the inter-patient variability, with a 22% greater steady state clearance (CLss) and an 18% greater volume of distribution (V) in males. However, results from the population analysis have shown that the differences in exposure are not significant (with an estimated median AUC and C_{max} of 11282 µg•d/mL and 578.9 µg/mL in females and 8451 µg•d/mL and 432.5 µg/mL in males, respectively at Cycle 6), indicating that there is no need to dose adjust based on gender.

Elderly

The population pharmacokinetic analysis of obinutuzumab showed that age did not affect the pharmacokinetics of obinutuzumab. No significant difference was observed in the pharmacokinetics of obinutuzumab among patients < 65 years (n=265), patients between 65-75 years (n=197) and patients > 75 years (n=128).

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of obinutuzumab in paediatric patients.

Renal impairment

The population pharmacokinetic analysis of obinutuzumab showed that creatinine clearance does not affect pharmacokinetics of obinutuzumab. Pharmacokinetics of obinutuzumab in patients with mild creatinine clearance (CrCl 50-89 mL/min, n=306) or moderate (CrCl 30 to 49 mL/min, n=72) renal impairment were similar to those in patients with normal renal function (CrCl ≥ 90 mL/min, n=207). Pharmacokinetic data in patients with severe renal impairment (CrCl 15-29 mL/min) is limited (n=5), therefore no dose recommendations can be made.

Hepatic impairment

No formal pharmacokinetic study has been conducted in patients with hepatic impairment.

5.3 Preclinical safety data

No studies have been performed to establish the carcinogenic potential of obinutuzumab.

No specific studies in animals have been performed to evaluate the effect of obinutuzumab on fertility. In repeat-dose toxicity studies in cynomolgus monkeys obinutuzumab had no adverse effects on male and female reproductive organs.

An enhanced pre and postnatal development (ePPND) toxicity study in pregnant cynomolgus monkeys showed no evidence of teratogenic effects. However, weekly obinutuzumab dosing from post-coitum day 20 to delivery resulted in complete depletion of B cells in infants at weekly intravenous obinutuzumab doses of 25 and 50 mg/kg (2-5 times the clinical exposure based on C_{max} and AUC). Offspring exposure on day 28 post-partum suggests that obinutuzumab can cross the blood-placenta barrier. Concentrations in infant serum on day 28 post-partum were in the range of concentrations in maternal serum, whereas concentrations in milk on the same day were very low (less than 0.5% of the corresponding maternal serum levels) suggesting that exposure of infants must have occurred in utero. The B cell counts returned to normal levels, and immunologic function was restored within 6 months post-partum.

In a 26-week cynomolgus monkey study, hypersensitivity reactions were noted and attributed to the foreign recognition of the humanised antibody in cynomolgus monkeys (0.7-6 times the clinical exposure based on C_{max} and AUC at steady state after weekly administration of 5, 25, and 50 mg/kg). Findings included acute anaphylactic or anaphylactoid reactions and an increased prevalence of

systemic inflammation and infiltrates consistent with immune-complex mediated hypersensitivity reactions, such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation. These reactions led to unscheduled termination of 6/36 animals treated with obinutuzumab during dosing and recovery phases; these changes were partially reversible. No renal toxicity with a causal relationship to obinutuzumab has been observed in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Trehalose dihydrate
Poloxamer 188
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years.

After dilution
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.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

40 mL concentrate in a 50 mL vial (clear Type I glass) with stopper (butyl rubber). Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for dilution
Gazyvaro should be prepared by a healthcare professional using aseptic technique. Do not shake the vial.

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. 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. For storage conditions of the infusion bags see section 6.3.

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

Do not use other diluents such as glucose (5%) solution (see section 6.2).

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.

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).

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/937/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Roche Diagnostics GmbH
Nonnenwald 2
82377 Penzberg
GERMANY

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
The Applicant shall submit the OS mature data of stage 2 of study BO21004/CLL11 in order to confirm the benefit of GClb for this endpoint. Subgroups OS analyses in the frail and unfit subsets shall also be provided.	31 January 2016
The Applicant shall submit the OS mature data of stage 1a of study BO21004/CLL11 in the ITT population, in the subgroups of ZAP70 positive patients and ZAP70 negative patients	31 January 2016

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Gazyvaro 1,000 mg concentrate for solution for infusion
Obinutuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 40 mL concentrate contains 1,000 mg obinutuzumab, corresponding to a concentration before dilution of 25 mg/mL

3. LIST OF EXCIPIENTS

L-histidine
L-histidine hydrochloride monohydrate
Trehalose dihydrate
Poloxamer 188
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1,000 mg/40 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous use after dilution
Do not shake the vial

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/937/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Gazyvaro 1,000 mg concentrate for solution for infusion
Obinutuzumab
Intravenous use

2. METHOD OF ADMINISTRATION

For intravenous use after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1,000 mg/40 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Gazyvaro 1,000 mg concentrate for solution for infusion
Obinutuzumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

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 is used together with another cancer medicine called chlorambucil to treat chronic lymphocytic leukaemia (CLL). CLL is a cancer of the blood which affects a type of white blood cell called "B lymphocytes". The affected B lymphocytes multiply too quickly and live too long. This means that there are too many of them circulating in your blood. CLL can also make your lymph nodes get larger. They are part of a network of vessels running round your body that is filled with clear watery fluid called "lymph".

Gazyvaro is used in adults:
- who have not had any treatment before, and
- who have other medical conditions which make it unlikely that they would be able to tolerate a full dose of another cancer medicine called fludarabine.

How Gazyvaro works
Gazyvaro binds to targets on the surface of the "B lymphocyte" cells and causes them to die. It is given with chlorambucil to people with CLL to help delay the time it takes for their disease to worsen.

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 about this you should ask your doctor or nurse.

Warnings and precautions
Talk to your doctor or nurse before you are given Gazyvaro if:
- you have an infection, or have had a long-lasting or repeating infection
- you have ever taken 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 change how you take these
- you have ever had heart problems
- you have ever had neurological problems (losing your memory, difficulties moving or feeling, sight problems)
- you have ever had breathing problems or lung problems
- you have ever had a liver disease called hepatitis B
- you are due to have a vaccine or may need 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.

Infusion reactions
Tell your doctor or nurse straight away if you get any of the infusion reactions listed at the top of section 4. Infusion reactions can happen during the infusion or any time in the 24 hours after the infusion.

If you get infusion reactions, 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 less likely to happen during the second and later infusions. Your doctor may decide not to continue with Gazyvaro treatment if you have a strong infusion reaction.

Before each infusion of Gazyvaro, you will be given medicines which help to reduce possible infusion reactions or a potentially life-threatening complication known as tumour lysis syndrome, which is caused by chemical disturbances in the blood caused by the breakdown of dying cancer cells (see section 3).

Progressive multifocal leukoencephalopathy (PML)
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 communicating, difficulty with walking or loss of vision. If you had these symptoms prior to treatment with Gazyvaro, tell your doctor immediately about any changes in these symptoms. You may need medical treatment.

Children and adolescents
This medicine should not be given to children or young people below 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 herbal medicines and other medicines you can obtain without a prescription.

Contraception
If you could become pregnant you have to use a reliable method of contraception while being treated with Gazyvaro and for 18 months after your last treatment with Gazyvaro.

Pregnancy
You must tell your doctor or nurse if you are pregnant, think you are pregnant or if you intend to become pregnant. Your doctor will weigh up the benefit to you against the risk to your baby of taking Gazyvaro while you are pregnant. If you become pregnant during treatment with Gazyvaro, tell your doctor or nurse as soon as possible, as treatment with Gazyvaro may have implications for your health or that of your baby.

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

Driving and using machines
Gazyvaro is unlikely to affect your ability to drive, cycle or use any tools or machines. However, infusion reactions are very common during the first infusion. If you get an infusion reaction (see section 4), do not drive or use machines until the reaction stops.

3. How Gazyvaro is given

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

The Gazyvaro dose
You will be given 6 treatment cycles of Gazyvaro. Each cycle lasts 28 days. On Day 1 of your first cycle, you will be given 100 mg of Gazyvaro very slowly and your doctor will monitor you carefully. If you do not have an infusion reaction during the infusion, you may be given the rest of your first dose (900 mg) on the same day. However, if you do have an infusion reaction, you will be given the rest of the first dose on Day 2. A typical schedule is shown below.

Your first cycle:
- Day 1 – 100 mg
- Day 2 or Day 1 (continued) – 900 mg
- Day 8 – 1,000 mg
- Day 15 – 1,000 mg

Your next cycles 2, 3, 4, 5 and 6:
- Day 1 – 1,000 mg.

Medicines given before each infusion
Before each infusion of Gazyvaro, you will be given medicines which help to reduce possible infusion reactions or tumour lysis syndrome. These may include:

- fluids
- medicines to reduce an allergic reaction (anti-histamines)
- medicines to reduce inflammation (corticosteroids)
- painkillers (analgesics)
- medicines to reduce a fever
- medicine to prevent tumour lysis syndrome (such as allopurinol).

If you forget to have Gazyvaro
For anticancer treatment to be fully effective, it is very important to follow the dosing schedule. Therefore, if you miss your appointment, make another one as soon as possible.

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 serious side effects have been reported with this medicine:

Infusion reactions (very common – these may affect more than 1 in 10 people): tell your doctor or nurse straight away if you get any of the following in the 24 hours following your infusion:

Most frequently reported:
- headache
- fever, flushing or chills
- feeling sick, vomiting
- shortness of breath
- low or high blood pressure
- your heart beating very fast
- diarrhoea

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

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

Progressive multifocal leukoencephalopathy (PML)
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 communicating
- difficulty with walking
- loss of vision

If you had these symptoms prior to treatment with Gazyvaro, tell your doctor immediately about any changes in these symptoms. You may need medical treatment.

Infections
You might get infections more easily following Gazyvaro therapy. Often these are colds, but there have been cases of more severe infections. Return of hepatitis B, a liver disease, has also been reported in patients who have had hepatitis B in the past.

Tell your doctor after your Gazyvaro treatment if you get any symptoms of an infection, for example
- fever
- cough
- sore throat
- burning pain when passing urine
- feeling weak or generally unwell.

Other side effects include:

Very common (may affect more than 1 in 10 people)
- fever
- diarrhoea
- shown in blood tests:
  - 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)
  - anaemia (low levels of red blood cells)

Common (may affect up to 1 in 10 people)
- urinary tract infection
- cold sores
- runny nose
- nose and/or throat inflammation
- cough
- joint or back pain
- muscle and bone pain in your chest
- weight increase
- irregular heart rhythm (atrial fibrillation)
- hair loss
- skin cancer (squamous cell carcinoma)
- constipation
- shown in blood tests:
  - low levels of lymphocytes (a type of white blood cells)
  - low levels of all types of white blood cell (combined)
  - increase in potassium, phosphate or uric acid - which can cause kidney problems (part of tumour lysis syndrome)

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 via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

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 L-histidine, L-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
Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Manufacturer
Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

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

België/Belgique/Belgien
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 818 44 44

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Danmark
Roche a/s
Tlf: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

Malta
(See United Kingdom)

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Ελλάδα
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0)1 47 61 40 00

Hrvatska
Roche d.o.o.
Tel: + 385 1 47 22 333

Ireland
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

Ísland
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Κύπρος
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 - 22 76 62 76

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

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

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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 for tumour lysis syndrome (TLS)
Prophylaxis with adequate hydration and administration of uricostatics (e.g. *allopurinol*) starting 12-24 hours prior to start of therapy is recommended for patients with high circulating lymphocyte count (> 25 x 10^9/L) to reduce the risk of tumour lysis syndrome.

Prophylaxis and premedication for infusion related reactions (IRRs)
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 infusion related reactions

Day of treatment cycle	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1: Day 1	All patients	Intravenous corticosteroid[1]	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	All patients	Intravenous corticosteroid[1]	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 8, Day 15	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]	Completed at least 1 hour prior to Gazyvaro infusion
Cycles 2-6: Day 1	All patients	Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyvaro infusion
	Patients with an IRR (Grade 1 or more) with the previous infusion	Anti-histaminic medicine[3]	

[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*

Dose
The recommended dose of Gazyvaro is shown in Table 2.

Cycle 1
The recommended dose of Gazyvaro is 1,000 mg administered over Day 1 and Day 2, 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 to 6
The recommended dose of Gazyvaro is 1,000 mg administered on Day 1.

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

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

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.

Table 3 Standard infusion rate in the absence of infusion reactions/hypersensitivity

Cycle	Day of treatment	Rate of infusion
Cycle 1	Day 1 (100 mg)	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2 (or Day 1 continued) (900 mg)	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.
	Day 8	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.
	Day 15	
Cycles 2-6	Day 1	

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 Table 3). The Day 1 (Cycle 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 Table 3). The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

Instructions for dilution

Gazyvaro should be prepared by a healthcare professional using aseptic technique. Do not shake the vial.

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. 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.