Gazyva®

Obinutuzumab

Concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Gazyva 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

Chronic Lymphocytic Leukaemia (CLL)

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

Follicular Lymphoma (FL)

Gazyva in combination with chemotherapy, followed by Gazyva maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.

Gazyva in combination with bendamustine followed by Gazyva monotherapy is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with a rituximab-containing regimen.

4.2 Posology and method of administration

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

Posology

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 treatment such as urate oxidase (e.g. *rasburicase*), starting 12-24 hours prior to start of Gazyva infusion as per standard practice (see section 4.4). Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate.

Prophylaxis and premedication for infusion related reactions (IRRs)

Premedication to reduce the risk of IRRs is outlined in Table 1 (see also section 4.4). 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 Gazyva intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyva infusion and for the first hour after administration (see section 4.4).

Table 1 Premedication to be administered before Gazyva infusion to reduce the risk of IRRs in patients with CLL and FL(see section 4.4)

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 Gazyva infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyva 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 Gazyva infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before Gazyva infusion
		Anti-histaminic medicine[3]	

Day of treatment cycle	Patients requiring premedication	Premedication	Administration
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 Gazyva 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 Gazyva infusion
		Oral analgesic/anti-pyretic[2] Anti-histaminic medicine[3]	At least 30 minutes before Gazyva 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 Gazyva, the corticosteroid can be administered as an oral medicinal product if given at least 60 minutes prior to Gazyva, in which case additional IV corticosteroid as premedication is not required.*

Dose

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

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

Cycle 1

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

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

Cycle	Day of treatment	Dose of Gazyva
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]See section 5.1 for information on chlorambucil dose

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

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

Follicular lymphoma

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

Patients with previously untreated follicular lymphoma

Induction (in combination with chemotherapy[2])
Gazyva 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 Gazyva 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 Gazyva in combination with chemotherapy (CHOP or CVP or bendamustine) should continue to receive Gazyva 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])
Gazyva 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 Gazyva in combination with bendamustine or have stable disease should continue to

receive Gazyva 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 Gazyva to be administered during induction treatment, followed by maintenance treatment

Cycle	Day of treatment	Dose of Gazyva
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]See section 5.1 for information on bendamustine dose

Duration of treatment
Induction treatment of approximately six months (six treatment cycles of Gazyva, each of 28 day duration when combined with bendamustine, or eight treatment cycles of Gazyva, 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).

Delayed or missed doses
If a planned dose of Gazyva is missed, it should be administered as soon as possible; do not omit it or wait until the next planned dose.
If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, requiring delay of treatment, these doses should be given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1.

During maintenance, maintain the original dosing schedule for subsequent doses.

Dose modifications during treatment (all indications)

No dose reductions of Gazyva are recommended.

For management of symptomatic adverse events (including IRRs), see paragraph below (Management of IRRs or section 4.4).

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 Gazyva has not been established in patients with severe renal impairment (CrCl < 30 mL/min) (see sections 4.8 and 5.2).

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

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

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

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

Instructions on the rate of infusion are shown in Tables 4-6.

Chronic lymphocytic leukaemia (CLL)

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 of 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 the 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 50 mg/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)

Gazyva 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, Gazyva may be administered as a short (approximately 90 minutes) 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="4">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></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 infusion at the standard 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 Gazyva 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 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 the 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).

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

Traceability

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

Based on a subgroup analysis in previously untreated follicular lymphoma, the efficacy in FLIPI low risk (0-1) patients is currently inconclusive (see section 5.1). A therapy choice for these patients should carefully consider the overall safety profile of Gazyva plus chemotherapy and the patient-specific situation.

Infusion related reactions

The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyva were IRRs, which occurred predominantly during infusion of the first 1,000 mg. IRRs may be related to cytokine release syndrome which has also been reported in Gazyva treated patients. In CLL patients who received the combined measures for prevention of IRRs (adequate corticosteroid, 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 IRRs of all Grades 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 Gazyva (see section 4.8).

In the majority of patients, irrespective of indication, 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 and/or high circulating lymphocyte count in CLL [$> 25 \times 10^9$/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). For management of IRRs see section 4.2 Posology and method of administration.

Patients must not receive further Gazyva 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 Gazyva intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyva 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

Hypersensitivity reactions with immediate (e.g. anaphylaxis) and delayed onset (e.g. serum sickness) have been reported in patients treated with Gazyva. Hypersensitivity may be difficult to clinically distinguish from IRRs. Hypersensitivity symptoms can occur after previous exposure and very rarely with the first infusion. If a hypersensitivity reaction is suspected during or after an infusion, the infusion must be stopped and treatment permanently discontinued. Patients with known hypersensitivity to obinutuzumab must not be treated (see section 4.3).

Tumour lysis syndrome (TLS)

TLS has been reported with Gazyva. Patients who are considered to be at risk of TLS (e.g. patients with a high tumour burden and/or a high circulating lymphocyte count [$> 25 \times 10^9$/L] and/or renal impairment [CrCl < 70 mL/min]) should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidate (e.g. rasburicase) starting 12-24 hours prior to the infusion of Gazyva as per standard practice (see section 4.2). 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. 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 Gazyva. 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 (G-CSF) 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 neutropenia lasting more than 1 week receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Antiviral and antifungal prophylaxis should also be considered (see section 4.2). 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) may occur. 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 Gazyva. 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 Gazyva. 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 any 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.

Coagulation abnormalities including disseminated intravascular coagulation (DIC)

DIC including fatal events, has been reported in clinical studies and in postmarketing surveillance in patients receiving Gazyva. The majority of cases involved non-overt DIC, with subclinical (asymptomatic) changes in platelets and laboratory coagulation parameters occurring within 1-2 days after the first infusion with spontaneous resolution usually occurring within one to two weeks, not requiring drug discontinuation or specific intervention. In some cases, the events were associated with IRRs and/or TLS. No specific baseline risk factors for DIC were identified. Patients suspected to have non-overt DIC should be monitored closely with coagulation parameters including platelets and clinical observation for signs or symptoms of overt DIC. Gazyva should be discontinued at first onset of suspected overt DIC and appropriate treatment initiated.

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 Gazyva (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

Gazyva should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyva 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 Gazyva therapy. Fatal infections have been reported.

Patients (CLL) with both CIRS > 6 and CrCl < 70 mL/min are more at risk of infections, including severe infections (see section 4.8). In the follicular lymphoma studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in the maintenance phase. During the follow-up phase, Grade 3-5 infections are observed more in patients who received Gazyva plus bendamustine in the induction phase.

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 Gazyva (see section 4.8). HBV screening should be performed in all patients before initiation of treatment with Gazyva. 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 Gazyva. 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 Gazyva (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 nonspecific 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 Gazyva 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 Gazyva 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 infants with live virus vaccines

Due to the potential depletion of B-cells in infants of mothers who have been exposed to Gazyva during pregnancy, infants 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. The safety and timing of vaccination should be discussed with the infant’s physician (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug-drug interaction studies have been performed, although limited drug-drug interaction sub-studies have been undertaken for Gazyva with bendamustine, CHOP, fludarabine and cyclophosphamide (FC), and chlorambucil.

A risk for interactions with other concomitantly used medicinal products cannot be excluded.

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 medicinal products known to be metabolised by these enzyme systems.

Co-administration with Gazyva had no effect on the pharmacokinetics of bendamustine, FC, chlorambucil or the individual components of CHOP. In addition, there were no apparent effects of bendamustine, FC, chlorambucil or CHOP on the pharmacokinetics of Gazyva.

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, bendamustine, CHOP or CVP may increase the risk of neutropenia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during and for 18 months after treatment with Gazyva.

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. Serum concentrations of obinutuzumab in offspring were similar to those in the mothers on day 28 post-partum, whereas concentrations in milk on the same day were very low, suggesting that obinutuzumab crosses the placenta (see section 5.3). There are no data from the use of obinutuzumab in pregnant women. Gazyva 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 infants due to the pharmacological properties of the product. Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Gazyva during pregnancy until the infant's B-cell levels are within normal ranges (see section 4.4).

Breast-feeding

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

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

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

Gazyva has no or negligible influence on the ability to drive and use machines. IRRs are very common during the first infusion of Gazyva, 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) from clinical trials were identified during induction, maintenance and follow up for indolent Non-Hodgkin lymphoma (iNHL) including FL; treatment and follow up for CLL in the three pivotal clinical studies:

- BO21004/CLL11 (N=781): Patients with previously untreated CLL
- BO21223/GALLIUM (N=1390): Patients with previously untreated iNHL (86% of the patients had FL)
- GAO4753g/GADOLIN (N=409): Patients with iNHL (81% of the patients had FL) who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

These trials investigated Gazyva in combination with chlorambucil for CLL and with bendamustine, CHOP or CVP followed by Gazyva maintenance therapy for iNHL. The studies BO21223/GALLIUM and GAO4753g/GADOLIN enrolled patients with iNHL including FL. Therefore, in order to provide the most comprehensive safety information, the analysis of ADRs presented in the following has been performed on the entire study population (i.e. iNHL).

Table 7 summarises all ADRs including those of the pivotal studies (BO21004/CLL11, BO21223/GALLIUM GAO4753g/GADOLIN) that occurred at a higher incidence (difference of ≥ 2%) compared to the relevant comparator arm in at least one pivotal study in:

- Patients with CLL receiving Gazyva plus chlorambucil compared with chlorambucil alone or rituximab plus chlorambucil (study BO21004/CLL11)
- Patients with previously untreated iNHL receiving Gazyva plus chemotherapy (bendamustine, CHOP, CVP) followed by Gazyva maintenance in patients achieving a response, compared to rituximab plus chemotherapy followed by rituximab maintenance in patients achieving a response (study BO21223/GALLIUM)
- Patients with iNHL who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen receiving Gazyva plus bendamustine, followed by Gazyva maintenance in some patients, compared to bendamustine alone (study GAO4753g/GADOLIN)

The incidences presented in Table 7 (all grades and Grades 3-5) are the highest incidence of that ADR reported from any of the three studies.

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), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Table 7 Summary of ADRs reported in patients[#] receiving Gazyva + chemotherapy*

System organ class Frequency	All Grades Gazyva + chemotherapy* (CLL, iNHL) followed by Gazyva maintenance (iNHL)	Grades 3-5[†] Gazyva + chemotherapy* (CLL, iNHL) followed by Gazyva maintenance (iNHL)
Infections and infestations		
Very common	Upper respiratory tract infection, sinusitis[§], urinary tract infection, pneumonia[§], herpes zoster[§], nasopharyngitis	
Common	Oral herpes, rhinitis, pharyngitis, lung infection, influenza	Urinary tract infection, pneumonia, lung infection, upper respiratory tract infection, sinusitis, herpes zoster
Uncommon	Hepatitis B reactivation	Nasopharyngitis, rhinitis, influenza, oral herpes
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Common	Squamous cell carcinoma of skin Basal cell carcinoma	Squamous cell carcinoma of skin Basal cell carcinoma
Blood and lymphatic system disorders		
Very common	Neutropenia[§], thrombocytopenia, anaemia, leukopenia	Neutropenia, thrombocytopenia
Common	Febrile neutropenia	Anaemia, leukopenia, febrile neutropenia
Uncommon	Disseminated intravascular coagulation[##]	
Metabolism and nutrition disorders		
Common	Tumour lysis syndrome, hyperuricaemia, hypokalaemia	Tumour lysis syndrome, hypokalaemia
Uncommon		Hyperuricaemia
Psychiatric disorders		
Very common	Insomnia	
Common	Depression, anxiety	
Uncommon		Insomnia, depression, anxiety
Nervous system disorders		
Very common	Headache	
Uncommon		Headache
Not known	Progressive multifocal leukoencephalopathy	
Cardiac disorders		
Common	Atrial fibrillation	Atrial fibrillation
Vascular disorders		
Common	Hypertension	Hypertension
Respiratory, thoracic and mediastinal disorders		
Very common	Cough[§]	
Common	Nasal congestion, rhinorrhoea, oropharyngeal pain	
Uncommon		Cough, oropharyngeal pain
Gastrointestinal disorders		
Very common	Diarrhoea, constipation[§]	
Common	Dyspepsia, haemorrhoids gastrointestinal perforation	Diarrhoea
Uncommon		Constipation, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common	Alopecia, pruritus	

System organ class Frequency	All Grades Gazyva + chemotherapy* (CLL, iNHL) followed by Gazyva maintenance (iNHL)	Grades 3-5† Gazyva + chemotherapy* (CLL, iNHL) followed by Gazyva maintenance (iNHL)
Common	Eczema	
Uncommon		Pruritus
Musculoskeletal and connective tissue disorders		
Very common	Arthralgia§, back pain , pain in extremity	
Common	Musculoskeletal chest pain, bone pain	Pain in extremity
Uncommon		Arthralgia, back pain, musculoskeletal chest pain, bone pain
Renal and Urinary Disorders		
Common	Dysuria, urinary incontinence	
Uncommon		Dysuria, urinary incontinence
General disorders and administration site conditions		
Very common	Pyrexia, Asthenia, fatigue	
Common	Chest pain	Pyrexia, asthenia, fatigue
Uncommon		Chest pain
Immune system disorders		
Rare	Cytokine release syndrome**	
Investigations		
Common	White blood cell count decreased, neutrophil count decreased, weight increased	White blood cell count decreased, neutrophil count decreased
Uncommon	Hypogammaglobulinemia	
Injury, poisoning and procedural complications		
Very common	IRRs	IRRs

Only the highest frequency observed in the trials is reported (based on studies BO21004/previously untreated CLL, BO21223/previously untreated advanced iNHL and GAO4753g/rituximab refractory iNHL)

Disseminated intravascular coagulation (DIC) including fatal events, has been reported in clinical studies and in postmarketing surveillance in patients receiving Gazyva (see section 4.4)

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

* Chemotherapy: Chlorambucil in CLL; bendamustine, CHOP, CVP in iNHL including FL

§ observed also during maintenance treatment with at least 2% higher incidence in Gazyva arm (BO21223)

**Based on clinical trial exposures in FL and CLL

The profile of adverse reactions in patients with FL was consistent with the overall iNHL population in both studies.

Description of selected adverse reactions

The incidences presented in the following sections if referring to iNHL are the highest incidence of that ADR reported from either pivotal study (BO21223/GALLIUM, GAO4753g/GADOLIN).

The study MO40597 was designed to characterize the safety profile of short duration infusions (approximately 90 minutes) from Cycle 2, in patients with previously untreated FL (see section 5.1 Pharmacodynamic properties).

Infusion related reactions

Most frequently reported (≥ 5%) symptoms associated with an IRR were nausea, vomiting, diarrhoea, headache, dizziness, fatigue, chills, pyrexia, hypotension, flushing, hypertension, tachycardia, dyspnoea, and chest discomfort. Respiratory symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and cardiac symptoms such as atrial fibrillation have also been reported (see section 4.4).

Chronic Lymphocytic Leukaemia

The incidence of IRRs was higher in the Gazyva plus chlorambucil arm compared to the rituximab plus chlorambucil arm. The incidence of IRRs was 66% with the infusion of the first 1,000 mg of Gazyva (20% of patients experiencing a Grade 3-4 IRR). Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyva. 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.

In patients who received the recommended measures for prevention of IRRs as described in section 4.2, a decreased incidence of IRRs of all Grades was observed. The rates of Grade 3-4 IRRs (which occurred in relatively few patients) were similar before and after mitigation measures were implemented.

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

Grade 3-4 IRRs occurred in 12% of patients. In Cycle 1, the overall incidence of IRRs was higher in patients receiving Gazyva plus chemotherapy compared to patients in the comparator arm. In patients receiving Gazyva plus chemotherapy, the incidence of IRRs was highest on Day 1 and gradually decreased with subsequent infusions. This decreasing trend continued during maintenance therapy with Gazyva alone. Beyond Cycle 1 the incidence of IRRs in subsequent infusions was comparable between the Gazyva and the relevant comparator arms. Overall, 4% of patients experienced an infusion related reaction leading to discontinuation of Gazyva.

Short Duration Infusion in patients with Follicular Lymphoma

In study MO40597 assessing the safety of SDI, a greater proportion of patients experienced any grade IRRs at Cycle 2 compared to the proportion who experienced IRRs after standard infusion at Cycle 2 in study BO21223 (10/99 [10.1%] vs. 23/529 [4.3%] respectively; IRRs attributed by the investigator to any component of study therapy). No patients experienced Grade ≥3 IRRs after SDI at Cycle 2 in MO40597; 3/529 (0.6%) experienced Grade ≥3 IRRs at Cycle 2 in study BO21223. IRR symptoms and signs were similar in both studies.
Infusion related reactions observed in Study MO40597/GAZELLE are summarized in Table 8.

Table 8 Study MO40597/GAZELLE Short-Duration Infusion: Infusion Related Reactions[a] by Cycle (Safety-Evaluable Population)

CTCAE Grade	C1 Overall (standard infusion)	C1[b] by day				C2[C]	C3	C4	C5	C6	C7	Over all induction cycles
		Day 1	Day 2[d]	Day 8	Day 15							
All Grade	65/113 (57.5%)	57/113 (50.4%)	4/51 (7.8%)	6/112 (5.4%)	5/111 (4.5%)	13/110 (11.8%)	9/108 (8.3%)	7/108 (6.5%)	6/107 (5.6%)	5/105 (4.8%)	2/55 (3.6%)	71/113 (62.8%)
Grade ≥3	6/113 (5.3%)	5/113 (4.4%)	1/51 (2.0%)	0	0	0	0	0	1/107 (0.9%)	0	0	7/113 (6.2%)

C=cycle; CTCAE = Common Terminology Criteria for Adverse Events; IRR=infusion related reaction
[a] Infusion related reaction defined as any event that occurred during or within 24 hours from the end of study treatment infusion that were judged by the investigator to be related to any components of therapy.
[b] C1 comprised three infusions at the standard infusion rate, administered at weekly intervals
[c] Patients received short-duration infusion from C2 onward. The denominator at C2 and subsequent cycles represents the number of patients who received SDI at that cycle.
[d] Patients treated with bendamustine on Cycle 1 Day 2.

Neutropenia and infections

Chronic Lymphocytic Leukaemia

The incidence of neutropenia was higher in the Gazyva plus chlorambucil arm (41%) 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 Gazyva 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 Gazyva plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the Gazyva plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported (see section 4.4).

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

In the Gazyva plus chemotherapy arm, the incidence of Grade 1-4 neutropenia (50%) was higher relative to the comparator arm with an increased risk during the induction period. The incidence of prolonged neutropenia and late onset neutropenia was 3% and 8%, respectively. The incidence of infection was 81% in the Gazyva plus chemotherapy arm (with Grade 3-5 events reported in 22% of patients and fatal events reported in 3% of patients). Patients who received G-CSF prophylaxis had a lower rate of Grade 3-5 infections (see section 4.4).

Short Duration Infusion in patients with Follicular Lymphoma

In study MO40597, assessing the safety of SDI, neutropenia was reported as an adverse event in a higher proportion of patients compared to study BO21223 in which patients receiving standard duration infusion 69/113 [61.1%] vs 247/595 [41.5%], respectively, throughout induction). The median and range of neutrophil count values were similar in both studies at each time point. Febrile neutropenia was reported in a similar proportion of patients in MO40597 and BO21223 (6/113 [5.3%] vs 31/595 [5.2%], respectively). Infection was reported less frequently in MO40597 than in BO21223 (45/113 [39.8%] vs 284/595 [47.7%], respectively).

Thrombocytopenia and haemorrhagic events

Chronic Lymphocytic Leukaemia

The incidence of thrombocytopenia was higher in the Gazyva plus chlorambucil arm compared to the rituximab plus chlorambucil arm (16% vs. 7%) especially during the first cycle. Four percent of patients treated with Gazyva plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the Gazyva infusion) (see section 4.4). The overall incidence of haemorrhagic events was similar in the Gazyva 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 Gazyva were reported in Cycle 1. No Grade 5 events of thrombocytopenia were reported. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

The incidence of thrombocytopenia was 15%. Thrombocytopenia occurred more frequently in Cycle 1 in the Gazyva plus chemotherapy arm. Thrombocytopenia occurring during or 24 hours from end of infusion (acute thrombocytopenia) was more frequently observed in patients in the Gazyva plus chemotherapy arm than in the comparator arm. The incidence of haemorrhagic events was similar across all treatment arms. Haemorrhagic events and Grade 3-5 haemorrhagic events occurred in 12% and 4% of patients, respectively. While fatal haemorrhagic events occurred in less than 1% of patients; none of the fatal adverse events occurred in Cycle 1.

Short Duration Infusion in patients with Follicular Lymphoma

In study MO40597, assessing the safety of SDI, thrombocytopenia was reported as an adverse event in a higher proportion of patients compared to study BO21223 in which patients received standard duration infusion (21/113 [28.6%] vs 63/595 [10.6%], respectively, throughout induction). The median and range of platelet count values were similar in both studies at each time point. No thrombocytopenia events reported in MO40597 were associated with bleeding.

Special populations

Elderly

Chronic Lymphocytic Leukaemia

In the pivotal BO21004/CLL11 study, 46% (156 out of 336) of patients with CLL treated with Gazyva plus chlorambucil were 75 years 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.

Indolent Non Hodgkin Lymphoma including Follicular Lymphoma

In the pivotal studies (BO21223/GALLIUM, GAO4753g/GADOLIN) in iNHL, patients 65 years or older experienced more serious adverse events and adverse events leading to withdrawal or death than patients < 65 years of age.

Renal impairment

Chronic Lymphocytic Leukaemia

In the pivotal BO21004/CLL11 study, 27% (90 out of 336) of patients treated with Gazyva plus chlorambucil had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than patients with a CrCl ≥ 50 mL/min (see section 4.2, 4.4 and 5.2). Patients with a CrCl < 30 mL/min were excluded from the study (see section 5.1).

Indolent Non Hodgkin Lymphoma including Follicular Lymphoma

In the pivotal studies (BO21223/GALLIUM, GAO4753g/GADOLIN) in iNHL, 5% (35 out of 698) and 7% (14 out of 204) of patients treated with Gazyva, respectively, had moderate renal impairment (CrCL < 50 mL/min). These patients experienced more serious adverse events, Grade 3 to 5 adverse events and adverse events leading to treatment withdrawal (patients in BO21223 only) than patients with a CrCl ≥ 50 mL/min (see section 4.2 and 5.2). Patients with a CrCl < 40 mL/min were excluded from the studies (see section 5.1).

Additional safety information from clinical studies experience

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 Gazyva (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 Gazyva.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: http://sideeffects.health.gov.il

4.9 Overdose

No experience with overdose is available from human clinical studies. In clinical studies with Gazyva, 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: L01FA03

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 ADCC and ADCP 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 in patients with CLL (BO21004/CLL11), 91% (40 out of 44) of evaluable patients treated with Gazyva were B-cell depleted (defined as CD19+ B-cell counts $< 0.07 \times 10^9$/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.

In the pivotal clinical study in patients with iNHL (GAO4753/GADOLIN), 97% (171 out of 176) of evaluable patients treated with Gazyva were B-cell depleted at the end of the treatment period, and 97% (61 out of 63) remained depleted for more than 6 months from the last dose. Recovery of B-cells was observed within 12-18 months of follow-up in 11% (5 out of 46) of evaluable patients.

Clinical efficacy and safety

Chronic Lymphocytic Leukaemia

A Phase III international, multicentre, open label, randomised, two-stage, three-arm clinical study (BO21004/CLL11) investigating the efficacy and safety of Gazyva plus chlorambucil (GClb) compared to rituximab plus chlorambucil (RClb) or chlorambucil (Clb) alone was conducted in patients with previously untreated CLL 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 randomised 2:2:1 to receive Gazyva plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1a compared Gazyva plus chlorambucil to chlorambucil alone in 356 patients and Stage 2 compared Gazyva plus chlorambucil to rituximab plus chlorambucil in 663 patients.

In the majority of patients, Gazyva 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 related reactions in patients, an amendment was implemented and 140 patients received the first Gazyva 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 Gazyva 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 arms. 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%).

Efficacy results for patients with previously untreated CLL are summarised in Table 9. Kaplan-Meier curves for progression-free survival (PFS) and Overall Survival (OS) are shown in Figures 1-4.

Table 9 Summary of efficacy from BO21004/CLL11 study

	Stage 1a		Stage 2	
	Chlorambucil N=118	**Gazyva + chlorambucil N= 238**	**Rituximab + chlorambucil N= 330**	**Gazyva + chlorambucil N= 333**
	22.8 months median observation time[g]		**18.7 months median observation time[g]**	
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 time to event (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 time to event (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	

	Stage 1a		Stage 2	
	Chlorambucil N=118	**Gazyva + chlorambucil N= 238**	**Rituximab + chlorambucil N= 330**	**Gazyva + chlorambucil N= 333**
	22.8 months median observation time[g]		**18.7 months median observation time[g]**	
Time to new anti-leukaemic therapy				
No. (%) of patients with event	65 (55.1%)	51 (21.4%)	86 (26.1%)	55 (16.5%)
Median time to event (months)	14.8	NR	30.8	NR
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	
Overall survival				
No. (%) of patients with event	57 (48.3%)	93 (39.1%)	147 (44.5%)	121 (36.3%)
Median time to event (months)	66.7	NR	73.1	NR
Hazard ratio (95% CI)	0.68 [0.49; 0.94]		0.76 [0.60; 0.97]	
p-value (Log-Rank test, stratified[b])	0.0196		0.0245	

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, MRD: Minimal Residual Disease, NR = Not reached

[a] Defined as the time from randomisation 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

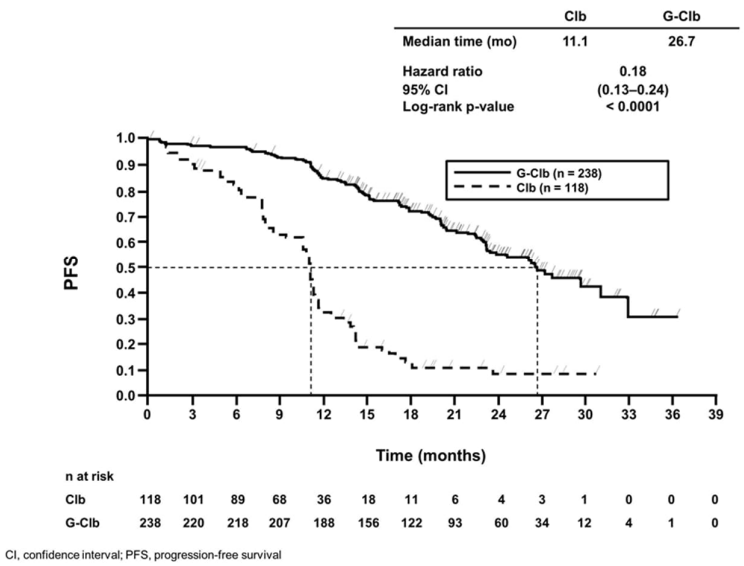
[f] Includes MRD positive patients and patients who progressed or died before the end of treatment

[g] Median observation time for overall survival (OS) data corresponds to 62.5 months median observation time in Stage 1a and to 59.4 months median observation time in Stage 2.

Results of subgroup analyses

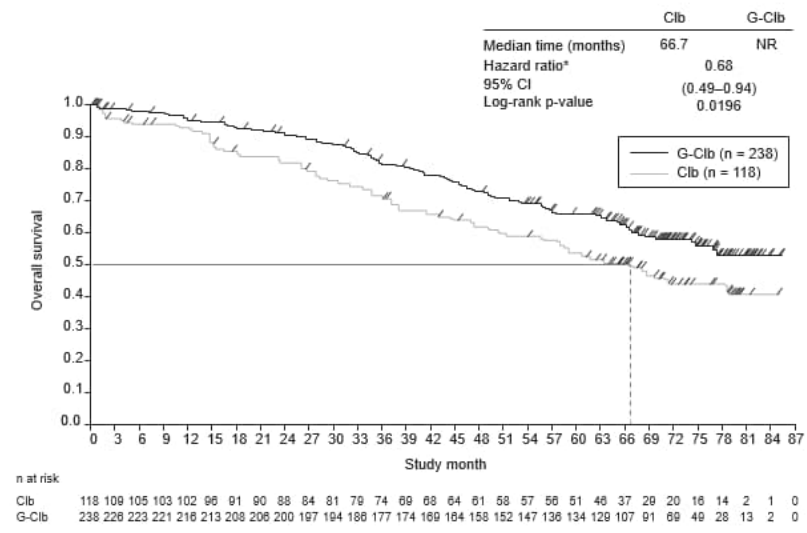
Results of the progression free survival (PFS) subgroup analysis (i.e. sex, age, Binet stages, CrCl, CIRS score, beta2-microglobulin, IGVH status, chromosomal abnormalities, lymphocyte count at baseline) were consistent with the results seen in the overall Intent-to-Treat population. The risk of disease 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 PFS from Stage 1a in patients with CLL (Study BO21004/CLL11)



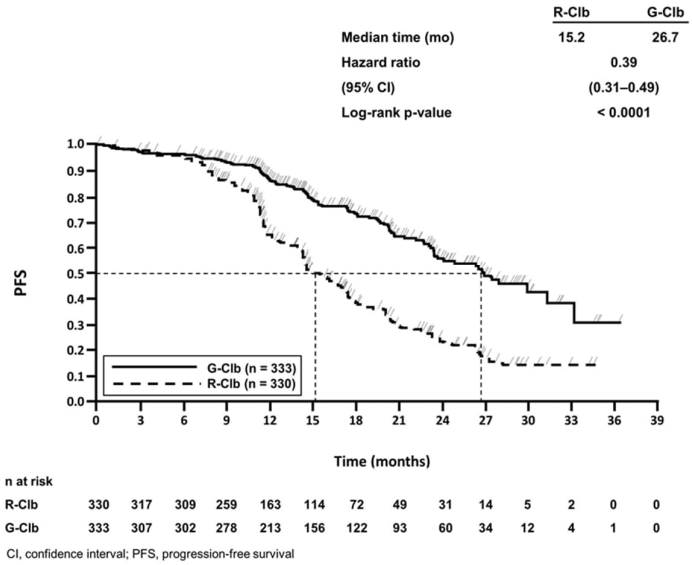
CI, confidence interval; PFS, progression-free survival

Figure 2 Kaplan-Meier curve of OS from Stage 1a in patients with CLL (Study BO21004/CLL11)



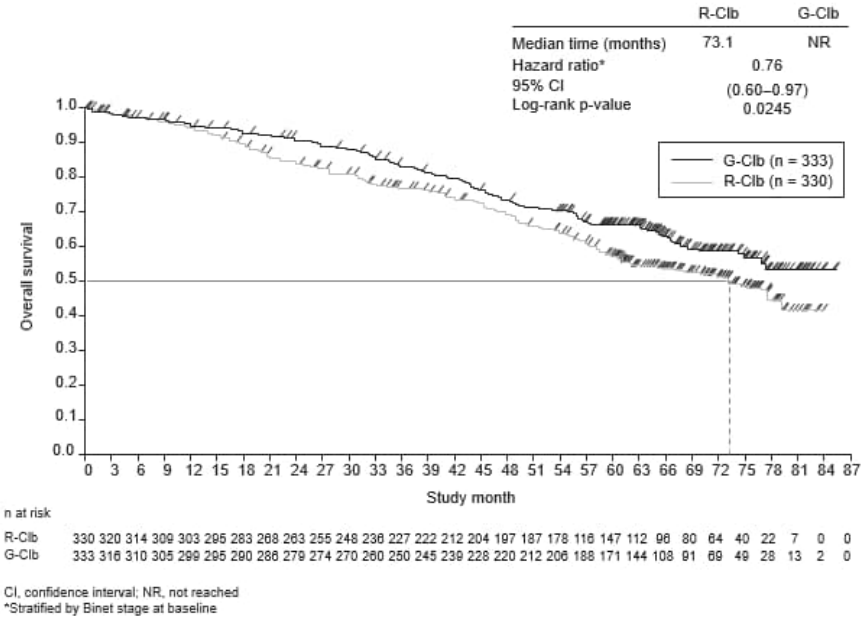
CI, confidence interval; NR, not reached
*Stratified by Binet stage at baseline

Figure 3 Kaplan-Meier curve of investigator assessed PFS from Stage 2 in patients with CLL (Study BO21004/CLL11)



CI, confidence interval; PFS, progression-free survival

Figure 4 Kaplan-Meier curve of OS from Stage 2 in patients with CLL (Study BO21004/CLL11)



CI, confidence interval; NR, not reached
*Stratified by Binet stage at baseline

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 Gazyva to a chlorambucil regimen does not increase the experience of fatigue for patients.

Follicular lymphoma

Previously untreated follicular lymphoma (study BO21223/GALLIUM)

In a phase III, open label, multicentre, randomised clinical study (BO21223/GALLIUM), 1202 patients with previously untreated Grade 1-3a advanced (stage II bulky disease, stage III/IV) FL were evaluated. Patients with FL Grade 3b were excluded from the study. Patients were randomised to 1:1 to receive either Gazyva (n=601 patients) or rituximab (n=601 patients) in combination with chemotherapy (bendamustine, CHOP or CVP), followed by Gazyva or rituximab maintenance in patients achieving a complete or partial response.

Gazyva was given by intravenous infusion as a dose of 1,000 mg on Days 1, 8 and 15 of Cycle 1, on Day 1 of subsequent cycles. In total, six cycles of Gazyva (every 28 days) were given in combination with six cycles of bendamustine, and a total of eight cycles of Gazyva (every 21 days) were given in combination with six cycles of CHOP or eight cycles of CVP. Gazyva was administered prior to chemotherapy. Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (Cycles 1-6) at 90 mg/m^2/day when given in combination with Gazyva. Standard dosing of CHOP and CVP was given. Following Cycles 6-8, in combination with chemotherapy, responding patients received Gazyva maintenance therapy every 2 months until disease progression or for up to 2 years.

The demographic data and baseline characteristics of the patient population were well balanced between the treatment arms; median age was 59 years, 81% were Caucasian, 53% were female, 79% had a FLIPI score of ≥ 2 and 7% had Stage II (bulky), 35% had Stage III and 57% had Stage IV disease, 44% had bulky disease (> 7 cm), 34% had at least one B-symptom at baseline and 97% had an ECOG performance status of 0-1 at baseline. Fifty-seven percent received bendamustine, 33% received CHOP, and 10% received CVP chemotherapy.

Efficacy results for patients with previously untreated FL are summarised in Table 10. Kaplan-Meier curves for progression-free survival (PFS) are shown in Figure 5.

Table 10 Summary of efficacy in patients with previously untreated FL from BO21223/ GALLIUM study

	Rituximab + Chemotherapy followed by rituximab maintenance N=601	**Gazyva +Chemotherapy followed by Gazyva maintenance N=601**
Primary Endpoint		
Investigator-assessed PFS[§] (PFS-INV) primary analysis		
Number (%) of patients with event	144 (24.0%)	101 (16.8%)
HR [95% CI]	0.66 [0.51, 0.85]	
p-value (Log-Rank test, stratified*)	0.0012	
3 year PFS estimate [%] [95% CI]	73.3 [68.8, 77.2]	80.0 [75.9, 83.6]
PFS-INV final analysis[§§]		
Number (%) of patients with event	244 (40.6%)	206 (34.3%)
HR [95% CI]	0.77 [0.64, 0.93]	
p-value (Log-Rank test, stratified*)	0.0055	
3 year PFS estimate [%] [95% CI]	75.5 [71.8, 78.9]	82.4 [79.0, 85.3]

	Rituximab + Chemotherapy followed by rituximab maintenance N=601	Gazyva +Chemotherapy followed by Gazyva maintenance N=601
7 year PFS estimate [%] [95% CI]	55.7 [51.3, 59.9]	63.4 [59.0, 67.4]
Key Endpoints		
IRC-assessed PFS (PFS-IRC) primary analysis		
Number (%) of patients with event	125 (20.8%)	93 (15.5%)
HR [95% CI]	0.71 [0.54, 0.93]	
p-value (Log-Rank test, stratified*)	0.0138	
Time to next anti-lymphoma therapy[#] primary analysis		
Number (%) of patients with event	111 (18.5%)	80 (13.3%)
HR [95% CI]	0.68 [0.51, 0.91]	
p-value (Log-Rank test, stratified*)	0.0094	
Overall Survival[#] primary analysis		
No. (%) of patients with event	46 (7.7%)	35 (5.8%)
HR [95% CI]	0.75 [0.49, 1.17][¶]	
p-value (Log-Rank test, stratified*)	0.21[¶]	
Overall Survival final analysis[§§]		
No. (%) of patients with event	86 (14.3%)	76 (12.6%)
HR [95% CI]	0.86 [0.63, 1.18]	
p-value (Log-Rank test, stratified*)	0.36	
Overall Response Rate at End of Induction[‡] (INV-assessed, CT) [#] primary analysis**		
Responders (%) (CR, PR)	522 (86.9%)	532 (88.5%)
Difference in response rate (%) [95% CI]	1.7% [-2.1%, 5.5%]	
p-value (Cochran-Mantel-Haenszel test)	0.33	
Complete Response (CR)	143 (23.8%)	117 (19.5%)
Partial Response (PR)	379 (63.1%)	415 (69.1%)

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Interval

* Stratification factors were chemotherapy regimen, FLIPI risk group for follicular lymphoma, geographic region

[§] Significance level at this efficacy interim analysis: primary analysis: 0.012, data cut-off 31 January 2016, median observation time 34/35 months

[§§] Final analysis, data cut-off 30 July 2021, median observation time 94 months

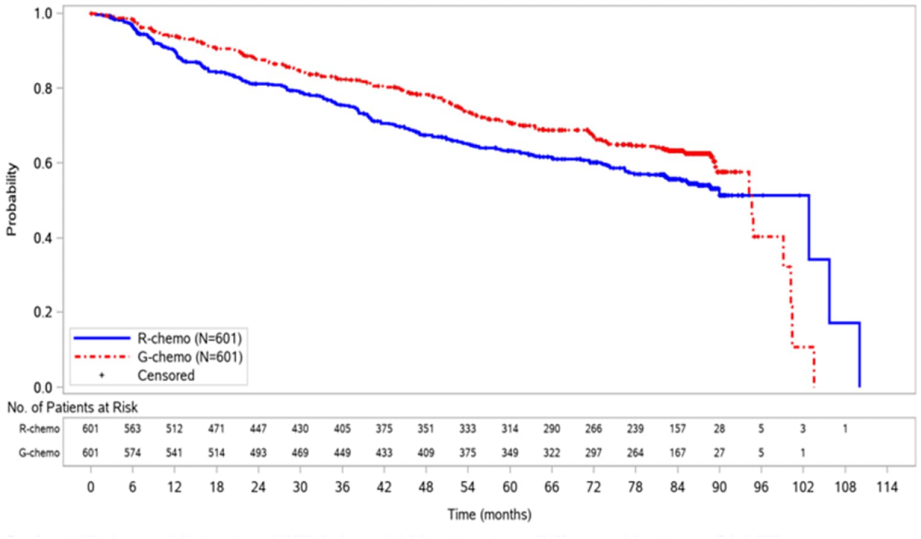
[¶] Data Not Yet Mature. Median was not reached at time of analysis

not adjusted for multiplicity

**Assessed as per modified Cheson 2007 criteria

[‡] End of Induction = end of induction phase, does not include monotherapy maintenance

Figure 5 Kaplan-Meier curve of INV-assessed progression-free survival in patients with previously untreated FL (Study BO21223/GALLIUM), final analysis*



R-Chemo: Rituximab plus chemotherapy, G-Chemo: Gazyva plus chemotherapy, HR: hazard ratio, CI: confidence interval

*Final analysis, data cut-off 30 July 2021, median observation time 94 months

Results of subgroup analyses

Results of subgroup analyses (not adjusted for multiplicity) were, in general, consistent with the results seen in the FL population, supporting the robustness of the overall result (primary analysis, data cut-off 31 January 2016). The subgroups evaluated included IPI, FLIPI, Bulky Disease, B Symptoms at baseline, Ann Arbor Stage and ECOG at baseline. In patients with FLIPI score 0-1 (low risk), no difference between Gazyva plus chemotherapy and rituximab plus chemotherapy was observed (INV-assessed PFS HR 1.17 (95%CI 0.63;2.19, 40 PFS events). This subgroup comprised 21% (253/1202) of the FL ITT population and experienced 16.3% (40/245) of the PFS events. In addition, exploratory subgroup analyses of PFS across chemotherapy regimens (bendamustine, CHOP and CVP) were consistent with the results seen in the Gazyva plus chemotherapy population. The observed HRs by chemotherapy subgroup were as follows; CHOP (n=398): HR 0.77 (95% CI: 0.50, 1.20), CVP (n=118): HR 0.63 (95% CI: 0.32, 1.21), and bendamustine (n=686): HR 0.61 (95% CI: 0.43, 0.86).

Patient Reported Outcomes

Based on the FACT-Lym questionnaire collected during treatment and follow-up phases, patients in both treatment arms experienced clinically meaningful improvements in lymphoma-related symptoms as defined by a ≥ 3 point increase from baseline in the Lymphoma subscale, a ≥ 6 point increase from baseline in the FACT Lym TOI and a ≥ 7 point increase from baseline in the FACT Lym Total score. EQ-5D utility scores were similar at baseline, during treatment and follow-up. No meaningful differences were seen between the arms in HRQOL or health status measures.

Due to the open label design the patient reported outcomes should be interpreted with caution.

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 (study GAO4753g/GADOLIN).

In a phase III, open label, multicentre, randomised clinical study (GAO4753g/GADOLIN), 396 patients with iNHL who had no response during treatment or who progressed within 6 months following the last dose of rituximab or a rituximab-containing regimen (including rituximab monotherapy as part of induction or maintenance treatment) were evaluated. Patients were randomised

1:1 to receive either bendamustine (B) alone (n = 202) or Gazyva in combination with bendamustine (G+B) (n = 194) for 6 cycles, each of 28 days duration. Patients in the G+B arm who did not have disease progression (i.e. patients with a complete response (CR), partial response (PR) or stable disease (SD)) at the end of induction continued receiving Gazyva maintenance once every two months for two years or until disease progression (whichever occurred first). Patients were stratified according to region, iNHL subtype (follicular versus non-follicular), rituximab-refractory type (whether refractory to prior rituximab monotherapy or rituximab in combination with chemotherapy) and the number of prior therapies (≤ 2 versus > 2).

The demographic data and baseline characteristics were well balanced between the treatment arms (median age 63 years, the majority were Caucasian [88%] and male [58%]). The majority of patients had follicular lymphoma (81%). The median time from initial diagnosis was 3 years and the median number of prior therapies was 2 (range 1 to 10); 44% of patients had received 1 prior therapy and 34% of patients had received 2 prior therapies.

Gazyva was given by intravenous infusion as a dose of 1,000 mg on Days 1, 8 and 15 of Cycle 1, on Day 1 of Cycles 2-6, and in patients who did not have disease progression, once every two months for two years or until disease progression (whichever occurs first). Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (Cycles 1-6) at 90 mg/m^2/day when given in combination with Gazyva or 120 mg/m^2/day when given alone. In patients treated with G+ B, 79.4% received all six treatment cycles compared to 66.7% of patients in the B arm.

The primary analysis based on independent Review Committee (IRC) assessment demonstrated a statistically significant - 45% reduction in the risk of disease progression or death, in patients with iNHL receiving G+B followed by Gazyva maintenance, compared with patients receiving bendamustine alone. The reduction in the risk of disease progression or death seen in the iNHL population is driven by the subset of patients with FL.

The majority of the patients in study GAO4753g had FL (81.1%). Efficacy results from the primary analysis in the FL population are shown in Table 11 and Figures 6 and 8. 11.6% of the patients had marginal zone lymphoma (MZL) and 7.1% had small lymphocytic lymphoma (SLL). In the non-FL population the HR for IRC-assessed PFS was 0.94 [95% CI: 0.49, 1.90]. No definitive conclusions could be drawn on efficacy in the MZL and SLL sub-populations.

At final analysis, the median observation time was 45.9 months (range: 0-100.9 months) for FL patients in the B arm and 57.3 months (range: 0.4-97.6 months) for patients in the G+B arm, representing an additional 25.6 months and 35.2 months of median follow-up in B and G+B arms, respectively, since the primary analysis. Only Investigator (INV) assessed endpoints were reported at final analysis since IRC assessments did not continue. Overall, the investigator assessed efficacy results were consistent with what was observed in the primary analysis. The overall survival (OS) in patients with FL was stable with longer follow-up (see Figure 7); the HR for risk of death was 0.71 (95%CI: 0.51, 0.98).

Table 11 Summary of primary efficacy analysis in patients with FL[#] from GAO4753g/GADOLIN study

	Bendamustine N=166	**Gazyva + Bendamustine followed by Gazyva maintenance N=155**
	Median observation time: 20 months	**Median observation time: 22 months**
Primary Endpoint in FL population		
IRC-assessed PFS (PFS-IRC)		
Number (%) of patients with event	90 (54.2%)	54 (34.8%)
Median time to event (months, 95% CI)	13.8 (11.4, 16.2)	NR (22.5,-)
HR (95% CI)	0.48 (0.34, 0.68)	
p-value (Log-Rank test, stratified*)	< 0.0001	
Secondary Endpoints		
Investigator-assessed PFS (PFS-INV)		
Number (%) of patients with event	102 (61.4%)	62 (40.0%)
Median time to event (months, 95% CI)	13.7 (11.0, 15.5)	29.2 (17.5,-)
HR (95% CI)	0.48 (0.35, 0.67)	
p-value (Log-Rank test, stratified*)	< 0.0001	
Best Overall Response (BOR) (IRC-assessed)[§]		
No. of patients included in the analysis	161	153
Responders (%) (CR/PR)	124 (77.0%)	122 (79.7%)
Difference in response rate (95% CI)	2.72 (-6.74, 12.18)	
p-value (Cochran-Mantel-Haenszel test)	0.6142	
Complete Responders (%)	31 (19.3%)	24 (15.7%)
Partial Responders (%)	93 (57.8%)	98 (64.1%)
Stable Disease (%)	18 (11.2%)	13 (8.5%)
Duration of response (DOR) (IRC-assessed)		
No of patients included in the analysis	127	122
No. (%) of patients with event	74 (58.3%)	36 (29.5%)
Median duration (months) of DOR (95% CI)	11.9 (8.8, 13.6)	NR (25.4,-)
HR (95% CI)	0.36 (0.24, 0.54)	

	Bendamustine N=166	**Gazyva + Bendamustine followed by Gazyva maintenance N=155**
	Median observation time: 20 months	**Median observation time: 22 months**
Overall Survival		
No. (%) of patients with event	36 (21.7%)	25 (16.1%)
Median time to event (months)	NR	NR
HR (95% CI)	0.71 (0.43, 1.19)	
p-value (Log-Rank test, stratified*)	0.1976	

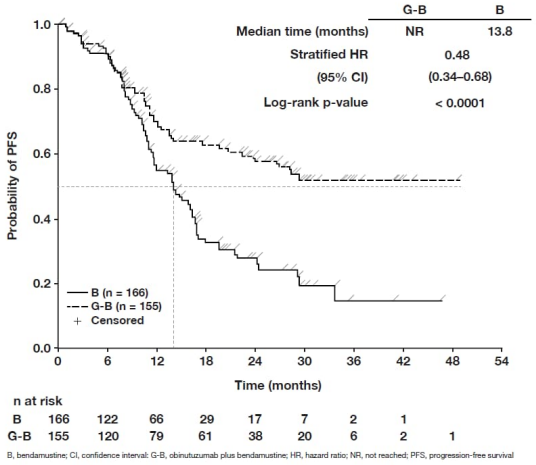
IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, NR = Not Reached

[#] Patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

*Stratification factors for analysis were refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs > 2). Follicular versus non-follicular was also a stratification factor for the study but is not applicable in the subgroup analysis of patients with FL.

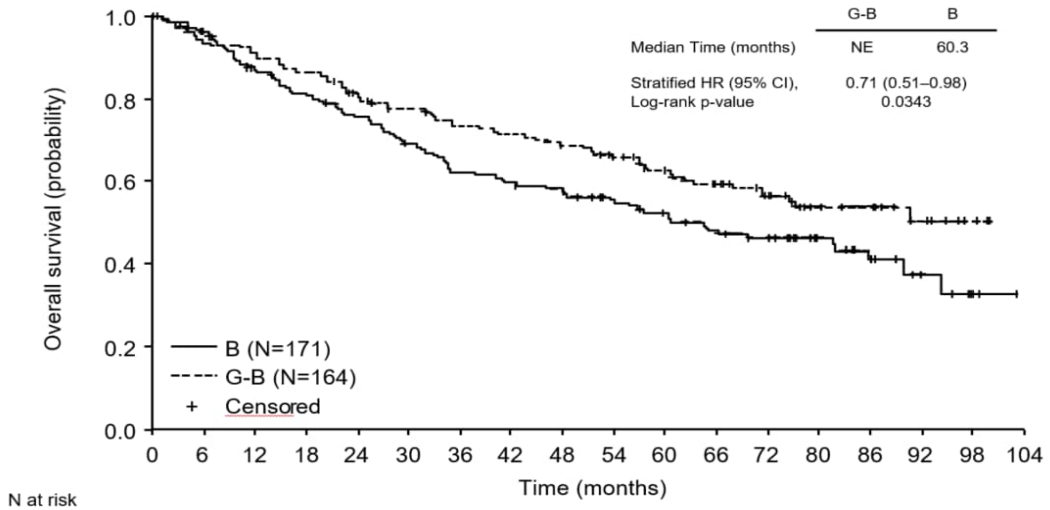
§ Best response within 12 months of start of treatment

Figure 6 Kaplan-Meier curve of IRC-assessed PFS in patients with FL [#] (Study GAO4753g/GADOLIN)



[#] Patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

Figure 7 Kaplan-Meier curve of Overall Survival in FL patients at Final Analysis (Study GAO4753g/GADOLIN)

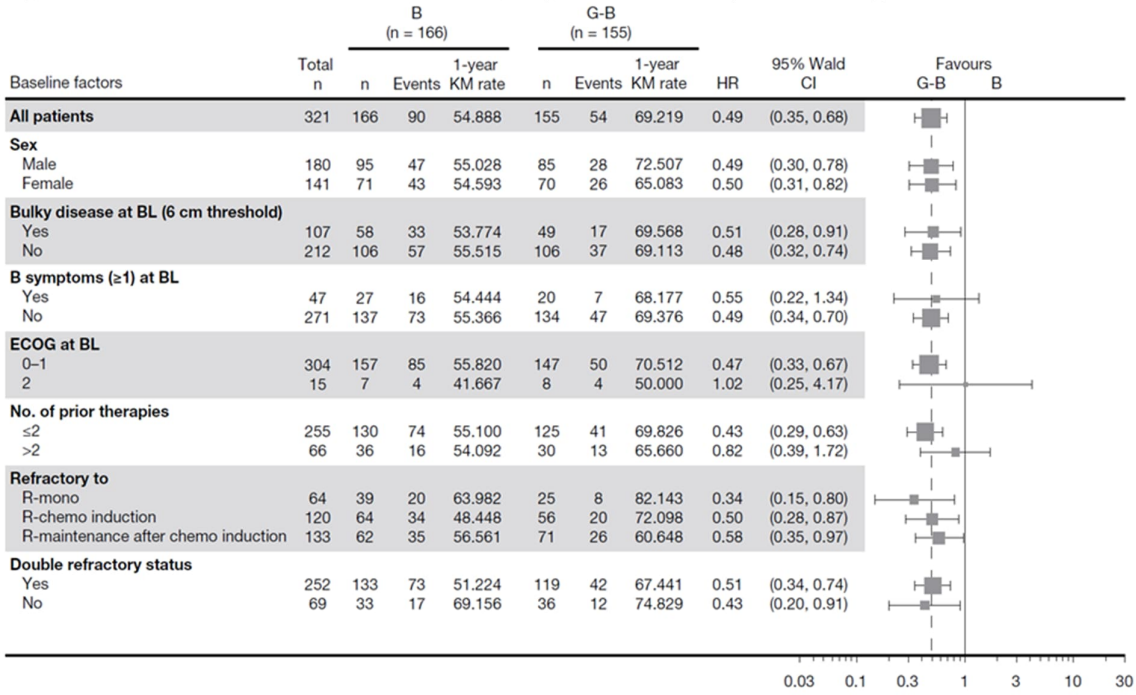


B, bendamustine; G-B, obinutuzumab plus bendamustine; HR, hazard ratio; NE, not estimated

Results of subgroup analyses

Results of subgroup analyses were in general consistent with the results seen in the FL population, supporting the robustness of the overall result.

Figure 8 IRC-assessed PFS by patient subgroup in FL *# (Study GAO4753g/GADOLIN)



Baseline factors	Total n	B (n = 166) n	B Events	B 1-year KM rate	G-B (n = 155) n	G-B Events	G-B 1-year KM rate	HR	95% Wald CI
All patients	321	166	90	54.888	155	54	69.219	0.49	(0.35, 0.68)
Sex									
Male	180	95	47	55.028	85	28	72.507	0.49	(0.30, 0.78)
Female	141	71	43	54.593	70	26	65.083	0.50	(0.31, 0.82)
Bulky disease at BL (6 cm threshold)									
Yes	107	58	33	53.774	49	17	69.568	0.51	(0.28, 0.91)
No	212	106	57	55.515	106	37	69.113	0.48	(0.32, 0.74)
B symptoms (≥1) at BL									
Yes	47	27	16	54.444	20	7	68.177	0.55	(0.22, 1.34)
No	271	137	73	55.366	134	47	69.376	0.49	(0.34, 0.70)
ECOG at BL									
0–1	304	157	85	55.820	147	50	70.512	0.47	(0.33, 0.67)
2	15	7	4	41.667	8	4	50.000	1.02	(0.25, 4.17)
No. of prior therapies									
≤2	255	130	74	55.100	125	41	69.826	0.43	(0.29, 0.63)
>2	66	36	16	54.092	30	13	65.660	0.82	(0.39, 1.72)
Refractory to									
R-mono	64	39	20	63.982	25	8	82.143	0.34	(0.15, 0.80)
R-chemo induction	120	64	34	48.448	56	20	72.098	0.50	(0.28, 0.87)
R-maintenance after chemo induction	133	62	35	56.561	71	26	60.648	0.58	(0.35, 0.97)
Double refractory status									
Yes	252	133	73	51.224	119	42	67.441	0.51	(0.34, 0.74)
No	69	33	17	69.156	36	12	74.829	0.43	(0.20, 0.91)

Unstratified HR is displayed. X-axis with logarithmic scale.
B, bendamustine; BL, baseline; chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; G-B, obinutuzumab plus bendamustine; HR, hazard ratio; KM, Kaplan-Meier; R-chemo, rituximab plus chemotherapy; R-maintenance, rituximab maintenance; R-mono, rituximab monotherapy

*pre-specified analyses performed on the intent to treat (ITT) population were repeated on the FL population; analysis of double refractory (i.e. unresponsive to or disease progression during or within 6 months of the last dose of an alkylating agent-based regimen) status was exploratory.
[#] Patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

Short Duration Infusion Study MO40597 (GAZELLE)

The safety of short (approximately 90 minutes) duration infusion (SDI) of obinutuzumab administered in combination with CHOP, CVP or bendamustine chemotherapy was evaluated in a multicenter, open-label, single arm study in 113 patients with previously untreated advanced follicular lymphoma (Study MO40597/GAZELLE).
Patients received the first cycle of obinutuzumab at the standard infusion rate on Day 1, 8, and 15 of Cycle 1. Patients who did not experience any Grade ≥3 IRRs during the first cycle received SDI from Cycle 2 onwards.
The primary endpoint of the study was the proportion of patients who experienced a Grade ≥3 IRR associated with SDI during Cycle 2, among those who had previously received 3 administrations of obinutuzumab at the standard infusion rate during Cycle 1 without experiencing a Grade ≥3 IRR.
No Grade ≥3 IRRs were observed among patients receiving SDI at Cycle 2. After Cycle 2 only one patient experienced a Grade 3 IRR (hypertension at Cycle 5). See section 4.8 Undesirable Effects.

Patient-reported Outcomes
Due to the open label design the patient reported outcomes should be interpreted with caution. Based on the FACT-Lym questionnaire and EQ-5D index scale collected during the treatment and during follow-up periods, health-related quality of life was generally maintained in the pivotal study with no meaningful difference between the arms. However, in patients with FL the addition of Gazyva to bendamustine delayed the time to worsening of health-related quality of life as measured by the FACT-Lym TOI score by 2.2 months (median 5.6 versus 7.8 months for B and G+B respectively HR = 0.83; 95% CI: 0.60, 1.13).

Immunogenicity

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

Patients in the CLL pivotal study BO21004/CLL11 were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Gazyva. In patients treated with Gazyva 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.

No post-baseline HAHA (Human Anti-Human Antibody) were observed in patients with iNHL treated in study GAO4753g/GADOLIN. In study BO21223/GALLIUM, 1/565 patient (0.2% of patients with a post-baseline assessment) developed HAHA at induction completion. While the clinical significance of HAHA is not known, a potential correlation between HAHA and clinical course cannot be ruled out.

5.2 Pharmacokinetic properties

A population pharmacokinetic (PK) model was developed to analyse the PK data in 469 iNHL, 342 CLL and 130 diffuse large B-cell lymphoma (DLBCL) patients from Phase I, Phase II and Phase III studies who received obinutuzumab alone or in combination with chemotherapy.

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 465.7 µg/mL and AUC(τ) value was 8961 µg•d/mL and in iNHL patients the estimated median C_{max} value was 539.3 µg/mL and AUC(τ) value was 10956 µg•day/mL.

Distribution

Following intravenous administration, the volume of distribution of the central compartment (2.98 L in patients with CLL and 2.97 in patients with iNHL), 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 was approximately 0.11 L/day in CLL patients and 0.08 L/day in iNHL patients with a median elimination t½ of 26.4 days in CLL patients and 36.8 days in iNHL patients. Obinutuzumab elimination comprises 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 initial treatment, the non-linear time-varying clearance pathway is dominant and is consequently the major clearance pathway. As treatment continues, 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 removal of obinutuzumab from the circulation. However, once the majority of CD20 cells are bound with obinutuzumab, the impact of TMDD on PK is minimised.

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 a 19% 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} in CLL patients 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 and AUC and C_{max} in iNHL of 13172 µg•d/mL and 635.7 µg/mL in females and 9769 µg•d/mL and 481.3 µg/mL in males, respectively), 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=375), patients between 65-75 years (n=265) and patients > 75 years (n=171).

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=464) or moderate (CrCl 30 to 49 mL/min, n=106) renal impairment were similar to those in patients with normal renal function (CrCl ≥ 90 mL/min, n=383). Pharmacokinetic data in patients with severe renal impairment (CrCl 15-29 mL/min) is limited (n=8), 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 infant monkeys 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

Trehalose dihydrate
L-histidine hydrochloride monohydrate
L-histidine
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
The expiry date of the product is indicated on the packaging materials

After dilution
In use stability (shelf life of the diluted product): dilution in the following infusion solution in polyolefine, polypropylene, polyvinylchloride, and polyethylene soft bag: sodium chloride 0.9%., chemical and physical in-use stability has been demonstrated for 24 hours at 28°C followed by 24 hours not above 30°C followed by the administration duration of max. 24 hours.

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

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

Dose of Gazyva to be administered	Required amount of Gazyva concentrate	Size of PVC or non-PVC polyolefin infusion bag
100 mg	4 mL	100 mL
900 mg	36 mL	250 mL
1000 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 Gazyva, in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of Gazyva 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 Pharmaceuticals (Israel) Ltd., P.O. Box 6391, Hod Hasharon, 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

153-41-34195-00

9. MANUFACTURER

F. Hoffmann-La Roche Ltd., Basel, Switzerland.

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