PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Gazyva® Concentrate solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gazyva contains obinutuzumab as the active substance.

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

Contains sugar, (trehalose)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gazyva is a clear, colourless to slightly brownish liquid free from visible particulate matter, supplied as a single 1 000 mg dose in a sterile, preservative free, non-pyrogenic 50 mL glass vial containing 40 mL of liquid concentrate (25 mg/mL).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Chronic Lymphocytic Leukaemia

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

Follicular Lymphoma

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

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

4.2 Posology and method of administration

General

Substitution of Gazyva with any other biological medicinal product requires the consent of the prescribing medical practitioner.

Gazyva should be administered as an intravenous infusion through a dedicated line in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced medical practitioner.

Gazyva infusions should not be administered as an intravenous push or bolus. Isotonic 0,9 % sodium chloride solution should be used as the infusion vehicle (see *Special Instructions for Use, Handling and Disposal in Section 6.6 below*).

For *Incompatibilities:* see section 6.2

Prophylaxis and Premedication for Tumour Lysis Syndrome (TLS)

Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 10^9/L) and/or renal impairment (CrCl <70 mL/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. *allopurinol*) or suitable alternative such as a urate oxidase (e.g. *rasburicase*), 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 (IRR)

Premedication to reduce the risk of infusion related reactions (see section 4.4) is outlined in Table 1. Corticosteroid premedication is recommended for FL patients and mandatory for CLL patients for the first infusion. Premedication for subsequent infusions and other premedication should be administered as described below.

Hypotension, as a symptom of IRR, 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 Infusion Related Reactions

Day of Treatment Cycle	**Patients requiring premedication**	**Premedication**	**Administration**
Cycle 1: CLL	All patients	Intravenous corticosteroid [1,2]	Completed at least 1 hour prior to Gazyva infusion.
Day 1 Day 2		Oral analgesic/ anti-pyretic[3]	At least 30 minutes before Gazyva infusion.
FL Day 1		Anti-histaminic[4]	
All subsequent infusions CLL and FL	Patients with no IRR during the previous infusion	Oral analgesic/ anti-pyretic[3]	At least 30 minutes before Gazyva infusion.
	Patients with an IRR (Grade 1 or 2) with the previous infusion	Oral analgesic/ anti-pyretic[3] Antihistaminic[4]	At least 30 minutes before Gazyva infusion
	Patients with a Grade 3 IRR with the previous infusion OR	Intravenous corticosteroid[1]	Completed at least 1 hour prior to Gazyva infusion.
		Oral analgesic/	

	Patients with lymphocyte counts >25 x 10^9/L prior to next treatment	anti-pyretic[3]	At least 30 minutes before Gazyva infusion
		Anti-histaminic[4]	

[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] *If a corticosteroid-containing chemotherapy regimen is administered on the same day as Gazyva, the corticosteroid can be administered as an oral medication if given at least 60 min prior to Gazyva, in which case additional IV corticosteroid as premedication is* not required.

[3] e.g. *1 000 mg acetaminophen/paracetamol*

[4] e.g. *50 mg diphenhydramine*

Standard Dosage

Chronic Lymphocytic Leukaemia in combination with chlorambucil [1]

Cycle 1

The recommended dosage of Gazyva is 1 000 mg administered over Day 1 and Day 2, and on Day 8 and Day 15 of the first 28 day treatment cycle as shown in Table 2.

Two infusion bags should be prepared for the first dose (100 mg for the first infusion and 900 mg for the second infusion. If the 100 mg dose is completed without modifications of the infusion rate or interruptions, the 900 mg dose can be administered on the same day (without dose delay) 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 900 mg infusion must be administered the following day (see Table 2).

Cycle 2-6

Table 2 Dose and infusion rate of Gazyva for patients with CLL

Day of Treatment Cycle		**Dose of Gazyva**	**Rate of infusion** **For management of IRRs that occur during infusion, refer to Table 4.**
Cycle 1	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2 or Day 1 (continued)	900 mg	If no IRR reaction occurred during the previous infusion, administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. If the patient experienced an IRR during the previous infusion, start administration at 25 mg/hr. The rate of infusion can be escalated in increments of up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1 000 mg	If no IRR occurred during the previous infusion where the final infusion rate was ≥ 100 mg/hr, infusions can be started at a rate of 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If the patient experienced an IRR during the previous infusion administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 15	1 000 mg	
Cycles 2–6	Day 1	1 000 mg	

Delayed or missed doses (CLL):

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

The recommended dosage of Gazyva is 1 000 mg administered intravenously according to Table 3.

Previously Untreated Follicular Lymphoma

For patients with previously untreated follicular lymphoma, 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 CHOP, followed by 2 additional cycles of Gazyva alone or,
- Eight 21 day cycles in combination with CVP.

Previously untreated patients who achieve a complete or partial response to Gazyva plus chemotherapy should continue to receive Gazyva (1 000 mg) alone as maintenance therapy once every 2 months until disease progression or for up to 2 years.

Relapsed/Refractory Follicular Lymphoma

For patients with follicular lymphoma who have relapsed after or who are refractory to rituximab or a rituximab-containing regimen, Gazyva should be administered in six 28 day cycles in combination with bendamustine[2].

Patients who achieve complete or partial response or have stable disease should continue to receive Gazyva 1 000 mg alone as maintenance therapy once every 2 months until disease progression or for up to 2 years.

Table 3 Dose and Infusion rate of Gazyva for patients with FL

Day of treatment cycle		**Dose of Gazyva**	**Rate of infusion** For management of IRRs that occur during infusion, refer to Table 4
Cycle 1	Day 1	1 000 mg	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.
	Day 8	1 000 mg	If no IRR or an IRR of Grade 1 occurred during the previous infusion, where the final infusion rate was ≥ 100 mg/hr, 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.
	Day 15	1 000 mg	
Cycles 2–6 or 2-8	Day 1	1 000 mg	
Maintenance for FL patients	Every 2 months until progression or up to 2 years	1 000 mg	

Delayed or missed doses (FL)

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.

Dosage modifications during treatment (all indications):

No dose reductions of Gazyva are recommended.

For management of symptomatic adverse events (including IRRs), see Table 4 below and section 4.4.

Table 4 Infusion Rate Modification Guidelines for Infusion Related Reactions (See section 4.4, *Infusion Related Reactions*)

Grade 4 (life-threatening)	Stop infusion and permanently discontinue therapy.
Grade 3 (severe)	Temporarily interrupt infusion and treat symptoms. • Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred). • If patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Tables 2, 3). • For CLL patients receiving the Cycle 1, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. • If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy.
Grade 1-2 (mild and moderate)	• Reduce infusion rate and treat symptoms. • Upon resolution of symptoms, continue infusion.

	• If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Tables 2, 3). • For CLL patients receiving Cycle 1, Day 1 dose split over 2 days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

Special Dosage Instructions

Children: The safety and efficacy of Gazyva in children below 18 years of age have not been established.

Elderly: No dose adjustment is required in patients ≥ 65 years of age (see Use in Special Populations, Geriatric/Elderly Use).

Renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment. Gazyva has not been studied in patients with a CrCl $\leqslant$ 30 mL/min (see Pharmacokinetics in Special Populations - Renal Impairment).

Hepatic Impairment: The safety and efficacy of Gazyva in patients with hepatic impairment have not been established.

4.3 Contraindications

- Gazyva is contraindicated in patients with a known hypersensitivity to obinutuzumab or to any of the excipients.
- Gazyva should not be used in patients with active infections.
- Gazyva should not be used in patients with active hepatitis B infections.
- Concomitant use of Gazyva with live attenuated vaccines.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

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.

General

Infusion Related Reactions (IRRs):

The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyva were infusion related reactions (IRRs) which occurred predominantly during the first 1 000 mg. In CLL patients who received the combined measures for prevention of IRRs (adequate corticosteroid, oral analgesic/anti-histamine, omission of antihypertensive medication) 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 (see section 4.2) should be followed. 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 IgE mediated allergic reactions (e.g. *anaphylaxis*). Patients with a high tumour burden and/or high circulating lymphocyte count in CLL (> 25 x 10^9/L)) may be at increased risk of severe IRR. See section 4.2 for information on prophylaxis and Table 4 *Infusion Rate Modification Guidelines for Infusion Related Reactions* on how to manage IRRs based on grade of reaction.

Patients should 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 medication.

Hypersensitivity Reactions:

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

Hypersensitivity may be clinically difficult to distinguish from infusion related reactions.

Tumour Lysis Syndrome (TLS):

Tumour lysis syndrome (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 x 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), prior to the infusion of Gazyva as described in section 4.2. All patients 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 administration of granulocyte colony-stimulating factors (G-CSF) should be considered. Any signs of concomitant infection should be treated as appropriate. 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.

Thrombocytopenia:

Severe and life threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with Gazyva. 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 medical practitioner. 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.

Worsening of Pre-existing Cardiac Conditions:

In patients with underlying cardiac disease, dysrrhythmias (such as atrial fibrillation and tachydysrrhythmia), 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.

In the FL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in maintenance. 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, which may result in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including Gazyva (see section 4.8). Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Gazyva. At minimum this should include HBsAg-status and 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):

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 (CSF testing for JC 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 Gazyva 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, the safety and timing of vaccinations with live virus vaccines should be discussed with the child's healthcare provider. Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Gazyva during pregnancy until the infants' B cell levels are within normal ranges (see section *Use in Special Populations - Pregnancy*).

Use in special populations

Paediatric use*:*

The safety and efficacy of Gazyva in children below 18 years of age have not been established.

Geriatric/Elderly Use*:*

Chronic Lymphocytic Leukaemia: In the pivotal CLL study, 46 % (156 out of 336) of patients treated with Gazyva plus chlorambucil were 75 years old or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than patients < 75 years of age. No significant differences in efficacy were observed between patients ≥ 75 years of age and those < 75 years of age (see section 5.1 – Clinical/ Efficacy studies).

Non-Hodgkin Lymphoma: In the pivotal study in iNHL, 44 % (85 out of 194) of patients treated with Gazyva plus bendamustine were 65 years of age or older. No clinically meaningful differences in safety and efficacy were observed between these patients and younger patients.

Renal Impairment:

Chronic Lymphocytic Leukaemia: In the pivotal study in CLL, 27 % (90 out of 336) of patients treated with Gazyva plus chlorambucil had moderate renal impairment (creatinine clearance (CrCl) < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than those associated with CrCl ≥ 50 mL/min. (see section 4.2 and Pharmacokinetics in Special Populations). No significant differences in efficacy were observed between patients with CrCl < 50 mL/min and those with CrCl ≥ 50 mL/min. Patients with CrCl < 30 mL/min were excluded from the study (see section 5.1 – Clinical/Efficacy studies).

Non-Hodgkin Lymphoma: In the pivotal studies in iNHL, 7,7 % patients (14 out of 204) and 5 % patients 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 withdrawal (patients in the previously untreated FL trial only) than those associated with CrCl ≥ 50 mL/min (see sections 4.1 and 5.2 - *Special Dosage Instructions* and *Pharmacokinetics in Special Populations*).

Patients with CrCl <40 mL/min were excluded from the studies (see *Efficacy/Clinical studies*).

4.5 Interaction with other medicines and other forms of interaction

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

Gazyva should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. Women of child bearing potential should use effective contraception while receiving Gazyva and for 18 months following treatment with Gazyva (see section 5.2 - *Pharmacokinetic Properties, Elimination*). Postponing vaccination with live vaccines should be considered for infants born to mothers who have been exposed to Gazyva during pregnancy until the infants B-cell levels are within normal ranges.

No studies in pregnant women have been performed. A reproduction study in cynomolgus monkeys showed no evidence of embryofoetal toxicity or teratogenic effects but resulted in a complete depletion of B-lymphocytes in offspring. B-cell counts returned to normal levels in the offspring, and immunologic function was restored within 6 months of birth. Furthermore, the serum concentrations of Gazyva 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 Gazyva crosses the placenta.

Lactation:

Since human IgG is secreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during Gazyva therapy and for 18 months after the last dose of Gazyva (see section 5.2 - *Pharmacokinetic Properties, Elimination*). Animal studies have shown excretion of Gazyva in breast milk.

Fertility and male contraception:

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

To date, no safety-related concern regarding male reproductive functions or contraception has been reported.

4.7 Effects on ability to drive and use machines

No studies on the effects of Gazyva on the ability to drive and to use machines have been performed. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

a. Summary of the safety profile:

Adverse drug reactions (ADRs) which were reported in patients are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been used for the classification of frequency:

Very common ≥ 1/10, Common ≥ 1/100 to < 1/10, Uncommon ≥ 1/1 000 to < 1/100, Rare ≥ 1/10 000 to < 1/1 000 and Very rare < 1/10 000. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The adverse drug reactions (ADRs) described in this section were identified during treatment and follow up in the three pivotal clinical studies:

- BO21004/CLL11, N=781, Patients with previously untreated CLL
- BO21223 N=1 390: Patients with previously untreated iNHL (86 % of the patients had FL)
- GAO4753g, N=409 patients, in previously untreated CLL patients, and indolent Non Hodgkin Lymphoma (iNHL) patients (81,1 % 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 different chemotherapeutic agents (chlorambucil for CLL, bendamustine for iNHL) and as maintenance monotherapy (in iNHL only). The protocol of study GAO4753g defined patients with iNHL including FL as the study population. 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 5 summarises the ADRs that occurred at a higher incidence (difference of ≥2 %) 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) and in patients with iNHL receiving Gazyva plus bendamustine, followed by Gazyva maintenance in some patients, compared to bendamustine alone (study GAO4753g).

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

b. Tabulated list of adverse reactions

Table 5 - Summary of ADRs reported with a higher incidence (difference of ≥ 2 %) 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, upper respiratory tract infection, sinusitis, lung infection, pneumonia, herpes zoster
Uncommon		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
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
Eye disorders		
Common	Ocular hyperaemia	
Cardiac disorders		
Common	Atrial fibrillation, cardiac failure	Cardiac failure, atrial fibrillation
Uncommon		
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	Diarrhoea
Uncommon		Constipation, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common	Alopecia, pruritus	
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	Asthenia, pyrexia, fatigue

Uncommon		Chest pain
Investigations		
Common	Decreased white blood cell count, decreased neutrophil count, increased weight	Decreased white blood cell count, decreased neutrophil count
Injury, poisoning and procedural complications		
Very common	Infusion related reactions	Infusion related reactions

#with a higher incidence (difference of ≥ 2 % between the treatment arms). 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)

† 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)

In study GAO4753g/GADOLIN, patients in the bendamustine arm received 6 months of induction treatment only, whereas after the induction period, patients in the Gazyva plus bendamustine arm continued with Gazyva maintenance treatment.

During the maintenance period in study GAO4753g/GADOLIN, the most common adverse reactions were cough (20 %), upper respiratory infections (12 %), neutropenia (13 %), sinusitis (10 %), diarrhoea (10 %), IRRs (8 %), nausea (9 %), fatigue (9 %), bronchitis (10 %), arthralgia (6 %), pyrexia (7 %), nasopharyngitis (7 %), urinary tract infections (7 %), vomiting (6 %), rash (6 %), pneumonia (5 %), dyspnoea (5 %) and pain in extremity (5 %). The most common Grade 3-5 adverse reactions were neutropenia (10 %), febrile neutropenia (2 %), and anaemia, thrombocytopenia, pneumonia, sepsis, upper respiratory tract infection, and urinary tract infection (all at 1 %).

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

c. Description of selected adverse events

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).

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 65 % 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.

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.

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).

Thrombocytopenia and haemorrhagic events

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.

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 sections 4.2, 4.4 and 5.2). Patients with a CrCl < 30 mL/min were excluded from the study (see section 5.1 - Pharmacodynamic properties).

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 than patients with a CrCl ≥ 50 mL/min (see sections 4.4 and 5.5). Patients with a CrCl < 40 mL/min were excluded from the studies (see section 5.1 - Pharmacodynamic properties).

Additional safety information from clinical studies experience:

Progressive multifocal leukoencephalopathy

PML has been reported in patients treated with Gazyva (see section 4.4).

Hepatitis B reactivation

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

GastroIntestinal Perforation

Cases of gastrointestinal perforation have been reported in patients receiving Gazyva, mainly in iNHL. In the pivotal studies in iNHL up to 1 % of patients experienced gastrointestinal perforation.

Worsening of pre-existing cardiac conditions

Cases of dysrrhythmias (such as atrial fibrillation and tachydysrrhythmia), 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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Report Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No experience with overdosage is available from human clinical trials. In clinical trials 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 should be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It selectively binds to the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, and causes destruction of these cells by the immune system.

In non-clinical 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, obinutuzumab mediates low degree of complement dependent cytotoxicity (CDC). In animal models, obinutuzumab mediates potent B cell depletion and anti-tumour efficacy.

In the clinical trial BO21004/CLL11, 91 % (40 out of 44) of evaluable patients treated with obinutuzumab were B cell depleted (defined as CD19+ B-cell counts < 0,07x 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 to 18 months of follow up in 35 % (14 out of 40) of patients without progressive disease and 13 % (5 out of 40) with progressive disease.

Clinical / Efficacy Studies

Chronic Lymphocytic Leukaemia

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

Prior to enrolment, patients had to have documented CD20+ CLL, and one or both of the following measures of coexisting medical conditions; comorbidity score [total Cumulative Illness Rating Scale (CIRS)] of greater than 6 or reduced renal function as measured by CrCl <70 mL/min.

Patients with inadequate liver function (NCICTC 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.

A total of 781 patients were randomised 2:2:1 to receive obinutuzumab plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1 compared obinutuzumab plus chlorambucil to chlorambucil alone in 356 patients and Stage 2 compared obinutuzumab plus chlorambucil to rituximab plus chlorambucil in 663 patients. Efficacy results are summarised in Table A and in Figures 1-3.

In the majority of patients, obinutuzumab 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 obinutuzumab dose administered over 2 days [Day 1 (100 mg) and Day 2 (900 mg)]. See section 4.2. For each subsequent treatment cycle (Cycles 2 to 6), patients received obinutuzumab 1 000 mg on Day 1 only. Chlorambucil was given orally at 0,5 mg/kg body weight on Day 1 and Day 15 of all treatment cycles (1 to 6).

The demographics data and baseline characteristics were well balanced between the treatment groups. The majority of patients enrolled were Caucasian (95 %) and male (61 %). The median

age was 73 years, with 44 % being 75 years or older. At baseline, 22 % 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 %, GI disorders 38 %, Metabolism and Nutrition disorders 40 %, Renal and Urinary disorders 38 % and Musculoskeletal and Connective Tissue disorders 33 %.

The primary endpoint of the study was investigator assessed progression-free survival (PFS-INV). In addition, an independent review committee (IRC) assessed all patients for progression and IRC assessed PFS (PFS-IRC) was evaluated.

Key secondary efficacy endpoints were end of treatment response rate, molecular remission at end of treatment (minimal residual disease status) and time to event endpoints (event-free survival, new anti-leukaemic therapy). Overall survival for Stage 2 is presented in Figure 1.

Table A 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				
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]	
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

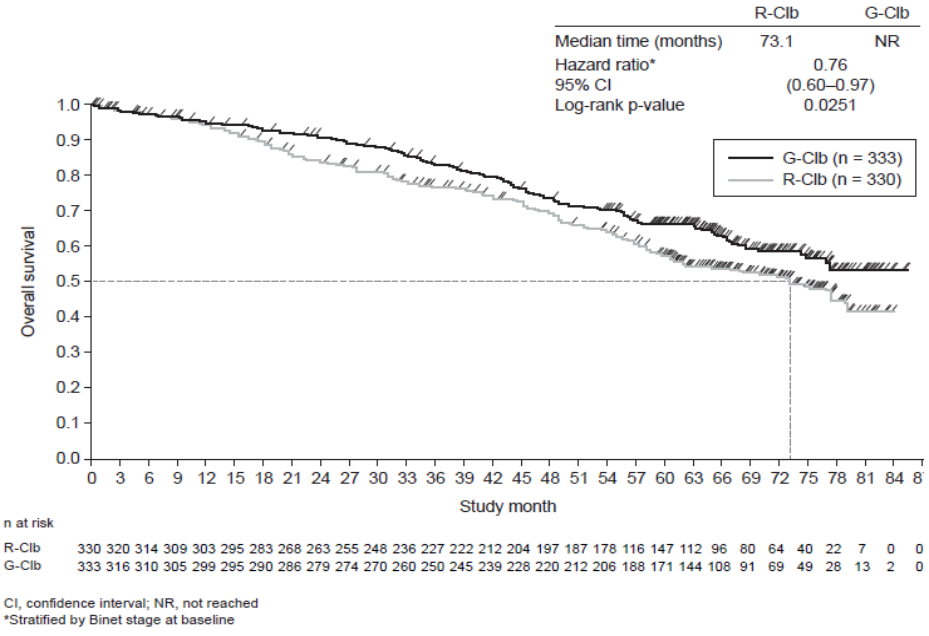
[e] MRD negativity is defined as a result below 0,0001

[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.

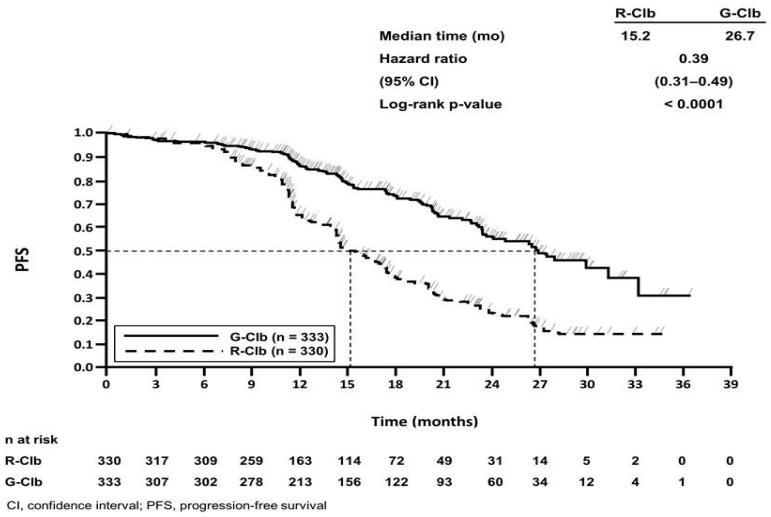
Results of the PFS subgroup analysis (i.e. sex, age, Binet stages, CrCl, CIRS score, beta2-microglobulin, IGVH status, chromosomal abnormalities, lymphocyte count at baseline) were consistent with the results seen in the overall Intent-to-Treat population. The risk of disease progression or death was reduced in the obinutuzumab plus chlorambucil arm (GClb) compared to the rituximab plus chlorambucil arm (RClb) and chlorambucil alone arm (Clb) in all subgroups. The Hazard Ratios ranged from 0,08 to 0,42 for GClb vs Clb and 0,28 to 0,71 for GClb vs RClb.

Figure 1 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

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



Non-Hodgkin Lymphoma (Follicular Lymphoma)

Previously Untreated Follicular Lymphoma

In a multicentre phase III, open-label, randomised study (BO21223/GALLIUM), 1202 previously untreated patients with stage II (bulky)/III/IV follicular lymphoma (FL) were evaluated. Patients were randomized 1:1 to receive either Gazyva or rituximab in combination with chemotherapy (CHOP, CVP, or bendamustine) followed by Gazyva or rituximab maintenance in patients who achieved a complete or partial response.

The demographic data and baseline characteristics of the FL population were well balanced [median age was 59 years, the majority of patients were Caucasian (81 %), and female (53 %)]. Seventy-nine percent had a FLIPI score of ≥ 2 and 7 % had Stage II (bulky), 35 % had Stage III and 57 % had Stage IV disease. Fifty-seven percent received bendamustine, 33 % received CHOP, and 10 % received CVP chemotherapy. Forty-four percent 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.

Gazyva (1 000 mg) was administered intravenously (as outlined in *Section 4.2 Dosage and Administration*) 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, when Gazyva was given in combination with chemotherapy, Gazyva maintenance therapy was given every 2 months for 2 years for responding patients or until disease progression.

Efficacy results are summarised in Table B. Kaplan-Meier curves for PFS are shown in Figure 4.

Table B Summary of efficacy in patients with FL from BO21223 (GALLIUM) study.

	Rituximab + Chemotherapy followed by rituximab maintenance N=601	**Gazyva + Chemotherapy followed by Gazyva maintenance N=601**
	Median observation time 34 months	**Median observation time 35 months**
Primary Endpoint		
Investigator-assessed PFS§ (PFS-INV)		
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	
2 year PFS estimate	80,9	87,7
[95% CI]	[77,4, 84.0]	[84,6, 90,1]
3 year PFS estimate	73,3	80,0
[95% CI]	[68,8, 77,2]	[75,9, 83,6]
Key Endpoints		
IRC-assessed PFS§ (PFS-IRC)		

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	
2 year PFS estimate	82,0	87,2
[95 % CI]	[78,5, 85,0]	[84,1, 89,7]
3 year PFS estimate	77,9	81,9
[95 % CI]	[73,8, 81,4]	[77,9, 85,2]
Time to next anti-lymphoma therapy		
Number (%) of patients with event	111 (18,5 %)	80 (1,3 %)
HR [95 % CI]	0,68 [0,51, 0,91]	
p-value (Log-Rank test, stratified*)	0,0094	
Overall Survival		
Number (%) 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 Response Rate at End of Induction‡ (INV-assessed, CT)**		
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 %)
95 % CI Clopper-Pearson	[20,4 %, 27,4 %]	[16,4 %, 22,9 %]
Partial Response (PR)	379 (63,1 %)	415 (69,1 %)
95 % CI Clopper-Pearson	[59,1 %, 66,9 %]	[65,2 %, 72,7 %]
Conversion Rate from End Of Induction		
Patients in PR at end of induction	222	271
Conversion from PR to CR	97 (43,7 %)	134 (49,4 %)
Difference in rate (%) [95 % CI]	5.7% [-3.1, 14.6%]	

Overall Response Rate at End of Maintenance		
Patients assessed at end of maintenance	533	525
Responders (%) (CR, PR)	341 (64,0 %)	371 (70,7 %)
Difference in response rate (%) [95 % CI]	6,7 % [1,0 %, 12,4 %]	
p-value (Cochran-Mantel-Haenszel test)	0,0197	
Complete response (CR)	195 (36,6 %)	205 (39,0 %)
95 % CI Clopper-Pearson	[32,5 %, 40.8 %]	[34,9 %, 43,4 %]
Partial response (PR)	146 (27,4 %)	166 (31,6 %)
95 % CI Clopper-Pearson	[23,7 %, 31,4 %]	[27,7 %, 35,8 %]

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

a) * Stratification factors were chemotherapy regimen, FLIPI risk group for follicular lymphoma, geographic region) [75]

b) ¶ Data Not Yet Mature. Median was not reached at time of analysis

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

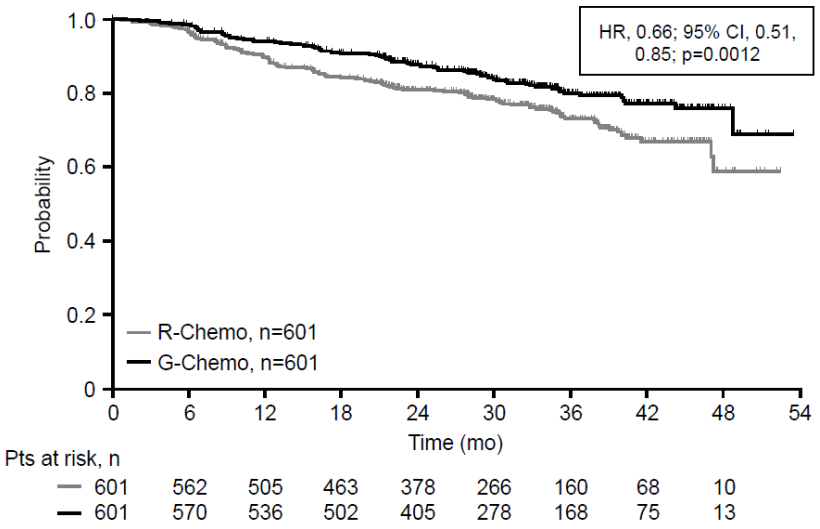
**Assessed as per modified Cheson 2007 criteria

§ Significance level at this efficacy interim analysis: 0.012

Response rates at the end of induction assessed by positron emission tomography (PET) were available for 297/601 patients in the Gazyva plus chemotherapy arm and 298/601 patients in the rituximab plus chemotherapy arm of the study. Complete response rates at end of induction as assessed by PET were 62,3 % in the Gazyva plus chemotherapy arm and 56,7 % in the rituximab

plus chemotherapy arm. Overall response rates were similar in the two arms, with a difference of 4,3 % in favour of the Gazyva plus chemotherapy arm (85,9 % for G-chemo vs 81,5 % for R-chemo).

Figure 4 Kaplan-Meier estimates of INV-assessed progression-free survival in FL patients



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

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. The subgroups evaluated included IPI, FLIPI, Chemo Regimen, Bulky Disease, B Symptoms at Baseline, Ann Arbor Stage and ECOG at Baseline.

Patient Reported Outcomes

Previously Untreated Follicular Lymphoma

Based on the FACT-Lym questionnaire collected during treatment and follow-up periods, both 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.

Relapsed/Refractory Follicular Lymphoma

In a phase III, open-label, multicentre, randomised study (GAO4753g/GADOLIN), 396 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 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 obinutuzumab maintenance until disease progression or for up to two years (whichever occurred first).

The demographic data and baseline characteristics were well balanced [median age was 63 years; the majority of patients were Caucasian (88 %) and male (58 %)]. 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.

Obinutuzumab was given intravenously as a 1 000 mg dose 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, every 2 months for up to 2 years or until disease progression. 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 obinutuzumab or 120 mg/m^2/day when given alone.

The primary analysis demonstrated a statistically significant and clinically meaningful 45 % reduction in the risk of disease progression (PD) or death, based on IRC assessment, in patients with iNHL receiving G+B followed by G maintenance vs B alone (stratified log-rank test p-value = 0,0001). IRC-assessed response rates at the end of induction treatment and IRC-assessed best overall response within 12 months of start of treatment were similar in the two treatment arms.

The majority of the patients had follicular lymphoma (FL) (81,1 %). Efficacy results from the primary analysis in the FL population are shown in Table C. Of the non-follicular patients, 11,6 %

had marginal zone lymphoma (MZL) and 7,1 % had small lymphocytic lymphoma (SLL). No conclusions could be drawn on efficacy in the MZL and SLL.

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 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).

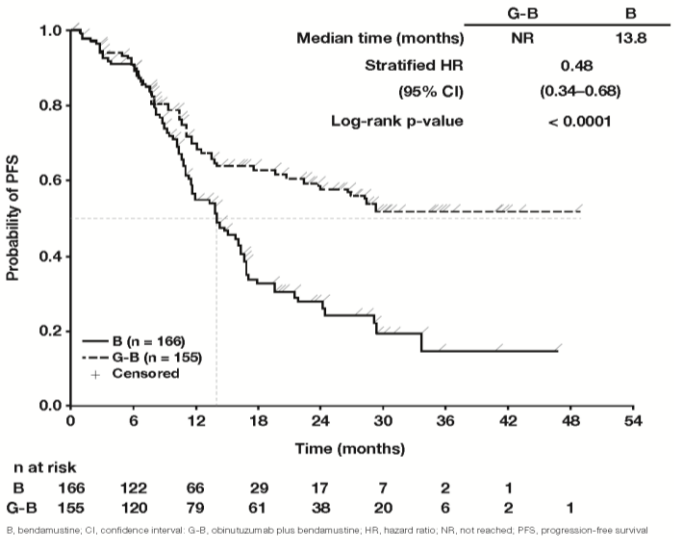
Table C Summary of primary efficacy analysis in FL patients from GAO4753g (GADOLIN) study

	Bendamustine N=166	**G+B 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 duration of PFS (months)	13,8	NR
HR [95 % CI]	0,48 [0,34; 0,68]	
p-value (Log-Rank test, stratified*)	<0,0001	

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

* * Stratification factors were iNHL subtype (follicular vs. non-follicular: not used in analysis of patients with FL), refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs. > 2)

Figure 3 Kaplan-Meier curve of IRC-assessed progression-free survival in FL patients



Patients in the CLL pivotal trial, BO21004/CLL11, were tested at multiple time-points for anti-therapeutic antibodies (ATA) to obinutuzumab. In obinutuzumab treated patients, 8 out of 140 in the randomised phase and 2 out 6 in the run-in phase tested positive for ATA at 12 months of follow-up. Of these patients, none experienced either 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.

Pharmacokinetic Properties

A population pharmacokinetic (PK) model was developed to analyse the PK data in 469 indolent Non Hodgkin Lymphoma (iNHL), 342 chronic lymphocytic leukaemia (CLL), and 130 Diffuse

Large B-cell lymphoma (DLBCL) patients from Phase I, Phase II and Phase III studies who received obinutuzumab.

Absorption

Obinutuzumab is administered intravenously. There have been no clinical 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 $AUC_{(\tau)}$ value was 8 961 µg.d/mL and in iNHL patients the estimated median C_{max} value was 539,3 µg/mL and $AUC_{(\tau)}$ value was 10 956 µg.d/mL.

Distribution

Following intravenous administration, the volume of distribution of the central compartment (2,72 L), approximates serum volume, which indicates distribution is largely restricted to plasma and interstitial fluid.

Metabolism

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.

Pharmacokinetics in Special Populations

In the population pharmacokinetic analysis, gender was found to be a covariate which explains some of the inter-patient variability, with a 18 % greater steady state clearance (CLss) and an 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 11 282 µg.d/mL and 578,9 µg/mL in females and 8 451 µg.d/mL and 432,5 µg/mL in males, respectively at Cycle 6 and AUC and C_{max} in iNHL patients of 13 172 µg.d/mL and 635,7 µg/mL in females and 9 769 µg.d/mL and 481,3 µg/mL in males, respectively), indicating that there is no need to dose adjust based on gender.

Elderly Population

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=454), patients between 65-75 years (n=317) and patients >75 years (n=190).

Paediatric Population

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

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=58), therefore no dosage recommendations can be made.

Hepatic impairment

No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with hepatic impairment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

L-histidine,

L-histidine hydrochloride monohydrate,

poloxamer 188,

trehalose dehydrate,

water for injections.

6.2 Incompatibilities

No incompatibilities between Gazyva and polyvinyl chloride or polyethylene or polypropylene or polyolefine bags or polyvinyl chloride (PVC) or polyurethane (PUR) or polyethylene (PE) infusion sets as well as optional inline filters with product contact surfaces of polyethersulfon (PES), a 3-way stopcock infusion aid made from polycarbonate (PC), and catheters made from polyetherurethane (PEU) have been observed in concentration ranges from 0,4 mg/mL to 20,0 mg/mL after dilution of Gazyva with 0,9 % sodium chloride. Diluted product should not be shaken or frozen.

Do not use other diluents such as Dextrose (5 %) solution to dilute Gazyva since its use has not been tested.

6.3 Shelf life

36 months

6.4 Special precautions for storage

For single use only. Discard any unused concentrate after initial opening. Store vials in a refrigerator at 2 °C - 8 °C. This medicine should not be used after the expiry date (EXP) shown on the pack. Keep vial in the outer carton in order to protect from light. Do not freeze. Do not shake.

Shelf-life of the solution for infusion containing the product

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C - 8 °C followed by 24 hours at ambient temperature (≤ 30 °C) followed by an infusion taking no longer than 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.

Gazyva does not contain antimicrobial preservatives. Therefore care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation.

6.5 Nature and contents of container

Pack of 1 vial in a carton. Clear colourless 50 mL Type I clear glass vial with a laminated grey butyl rubber stopper. A two piece crimp closure for the vial consists of a silver aluminium metal cap with rolled-in centre hole which is sealed with a red plastic flip-off disc.

6.6 Special Instructions for Use, Handling and Disposal

Instructions for dilution: **Gazyva should be prepared by a healthcare professional using aseptic technique.**

For CLL cycle 2-6 and FL cycles

Withdraw 40 mL of Gazyva liquid concentrate from the vial and dilute in PVC or non-PVC polyolefin infusion bags containing sterile, non-pyrogenic 0,9 % aqueous sodium chloride solution.

For preparation of infusion bags for CLL only, Cycle 1, Day 1 dose administered over 2 days.

To ensure differentiation of the two infusion bags for the initial 1 000 mg dose, the recommendation is 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 Gazyva liquid concentrate from vial and dilute 4 mL into a 100 mL infusion bag and the remaining 36 mL in a 250 mL PVC or non-PVC polyolefin infusion bags containing sterile, non-pyrogenic 0,9 % aqueous sodium chloride solution. Clearly label each infusion bag.

Dose of Gazyva to be Administered	**Required Amount of Gazyva Liquid Concentrate**	**Size of PVC or non-PVC polyolefin infusion bag**
100 mg	4 mL	100 mL
900 mg	36 mL	250 mL
1 000 mg	40 mL	250 mL

Do not use other diluents such as Dextrose (5 %) solution (see *Incompatibilities*).

The bag should be gently inverted to mix the solution in order to avoid excessive foaming.

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

Disposal of unused/expired medicines: The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road

Hertford Office Park

Building E

Vorna Valley

Midrand

Gauteng

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER

49/30.1/1142

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 24 March 2020

10. DATE OF REVISION OF THE TEXT

Last revision: 10 June 2022