

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Gazyvaro 1,000 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly brownish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Chronic Lymphocytic Leukaemia (CLL)

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

Follicular Lymphoma (FL)

Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced follicular lymphoma. (see section 5.1)

Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance 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 rituximab or a rituximab-containing regimen.

4.2 Posology and method of administration

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

Posology

Prophylaxis and premedication for tumour lysis syndrome (TLS)

Patients with a high tumour burden and/or a high circulating lymphocyte count ($> 25 \times 10^9/L$) and/or renal impairment ($CrCl < 70 \text{ mL/min}$) 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 Gazyvaro 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 infusion related reactions 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 Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration (see section 4.4).

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

¹100 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

⁴If a corticosteroid-containing chemotherapy regimen is administered on the same day as Gazyvaro, the corticosteroid can be administered as an oral medication if given at least 60 minutes prior to Gazyvaro, in which case additional IV corticosteroid as premedication is not required.

Dose

Chronic lymphocytic leukaemia (CLL, in combination with chlorambucil¹)

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

Cycle 1

The recommended dose of Gazyvaro in combination with chlorambucil is 1,000 mg administered over Day 1 and Day 2, (or Day 1 continued), and on Day 8 and Day 15 of the first 28 day treatment cycle.

Two infusion bags should be prepared for the infusion on Days 1 and 2 (100 mg for Day 1 and 900 mg for Day 2). If the first bag is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions and medical supervision are available

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

Cycles 2 - 6

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

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

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

¹See 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 Gazyvaro is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for Gazyvaro should be maintained between doses.

Follicular lymphoma

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

Patients with previously untreated follicular lymphoma

Induction (in combination with chemotherapy)²

Gazyvaro should be administered with chemotherapy as follows:

- Six 28-day cycles in combination with bendamustine² or,
- Six 21-day cycles in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP), followed by 2 additional cycles of Gazyvaro alone or,
- Eight 21-day cycles in combination with cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone(CVP).

Maintenance

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

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

Induction (in combination with bendamustine²)

Gazyvaro should be administered in six 28-day cycles in combination with bendamustine².

Maintenance

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

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

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

²See section 5.1 for information on bendamustine dose

Duration of treatment

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

Delayed or missed doses

If a planned dose of Gazyvaro 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 Gazyvaro 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 Gazyvaro 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 Gazyvaro in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.

Paediatric population

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

Method of administration

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

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

Instructions on the rate of infusion are shown in Tables 4-5.

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

Cycle	Day of treatment	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”.
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 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.
	Day 8 (1,000 mg)	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.
	Day 15 (1,000 mg)	
Cycles 2-6	Day 1 (1,000 mg)	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.

Table 5 Follicular lymphoma: Standard infusion rate in the absence of IRRs /hypersensitivity and recommendations in case an IRR occurred with previous infusion

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

Management of IRRs (all indications)

Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations of Gazyvaro as outlined below (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 and 5). 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 and 5). 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trade name 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 Gazyvaro plus chemotherapy and the patient-specific situation.

Infusion Related Reactions

The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyvaro were IRRs, which occurred predominantly during infusion of the first 1,000 mg. IRRs may be related to cytokine release syndrome which has also been reported in Gazyvaro 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 Gazyvaro (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 Gazyvaro infusions if they experience:

- acute life-threatening respiratory symptoms,
- a Grade 4 (i.e. life threatening) IRR or,
- a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion).

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension may occur during Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.

Hypersensitivity reactions

Hypersensitivity reactions with immediate (e.g. anaphylaxis) and delayed onset (e.g. serum sickness) have been reported in patients treated with Gazyvaro. Hypersensitivity may be difficult to clinically distinguish from infusion related reactions. 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)

Tumour lysis syndrome (TLS) has been reported with Gazyvaro. Patients who are considered to be at risk of TLS (e.g. patients with a high tumour burden and/or a high circulating lymphocyte count [$> 25 \times 10^9/L$] and/or renal impairment [$CrCl < 70 \text{ mL/min}$]) should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative such as a urate oxidase (e.g. rasburicase) starting 12-24 hours prior to the infusion of Gazyvaro 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 Gazyvaro. Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. If treatment is necessary it should be administered in accordance with local guidelines and the administration of granulocyte-colony stimulating factors (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 ($CrCl < 50 \text{ mL/min}$) are more at risk of neutropenia (see section 4.8).

Thrombocytopenia

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

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of 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, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyvaro (see section 4.8). These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition these patients should be hydrated with caution in order to prevent a potential fluid overload.

Infections

Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro in patients with a history of recurring or chronic infections. Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Gazyvaro therapy. Fatal infections have been reported.

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

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with Gazyvaro (see section 4.8). The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. The symptoms of PML are 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 Gazyvaro should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Immunisation

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

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

Due to the potential depletion of B-cells in infants of mothers who have been exposed to Gazyvaro 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 Gazyvaro 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 drugs known to be metabolised by these enzyme systems.

Co-administration with Gazyvaro 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 Gazyvaro.

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 Gazyvaro.

Pregnancy

A reproduction study in cynomolgus monkeys showed no evidence of embryofoetal toxicity or teratogenic effects but resulted in a complete depletion of B-lymphocytes in offspring. B-cell counts returned to normal levels in the offspring, and immunologic function was restored within 6 months of birth. 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. Gazyvaro should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

In case of exposure during pregnancy, depletion of B-cells may be expected in 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 Gazyvaro 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 Gazyvaro therapy and for 18 months after the last dose of Gazyvaro.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The adverse drug reactions (ADRs) described in this section were identified during 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=392): 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 Gazyvaro in combination with chlorambucil for CLL and with bendamustine, CHOP or CVP followed by Gazyvaro 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 6 summarises the ADRs of the pivotal studies (BO21004/CLL11, BO21223/GALLIUM GAO4753g/GADOLIN) that occurred at a higher incidence (difference of $\geq 2\%$) compared to the relevant comparator arm in at least one pivotal study in:

- Patients with CLL receiving Gazyvaro plus chlorambucil compared with chlorambucil alone or rituximab plus chlorambucil (study BO21004/CLL11)
- Patients with previously untreated iNHL receiving Gazyvaro plus chemotherapy (bendamustine, CHOP, CVP) followed by Gazyvaro 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 Gazyvaro plus bendamustine, followed by Gazyvaro maintenance in some patients, compared to bendamustine alone (study GAO4753g/GADOLIN)

The incidences presented in Table 6 (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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

Table 6 Summary of ADRs reported with a higher incidence (difference of $\geq 2\%$ versus the comparator arm) in patients[#] receiving Gazyvaro + chemotherapy*

Frequency	All Grades Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)	Grades 3-5 [†] Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)
Infections and infestations		
Very common	Upper respiratory tract infection, sinusitis [§] , , urinary tract infection, pneumonia [§] herpes zoster [§]	
Common	Oral herpes, rhinitis, pharyngitis, lung infection, influenza nasopharyngitis	Urinary tract infection, pneumonia, lung infection, upper respiratory tract infection, sinusitis, herpes zoster
Uncommon		Nasopharyngitis, rhinitis, influenza, oral herpes
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Common	Squamous cell carcinoma of skin	Squamous cell carcinoma of skin
Blood and lymphatic system disorders		
Very common	Neutropenia [§] , thrombocytopenia, anaemia, leukopenia	Neutropenia, thrombocytopenia
Common	Lymph node pain	Anaemia, leukopenia
Metabolism and nutrition disorders		
Common	Tumour lysis syndrome, hyperuricaemia, hypokalaemia	Tumour lysis syndrome, hypokalaemia
Uncommon		Hyperuricaemia
Nervous system disorders		
Very common	Headache	
Uncommon		Headache
Psychiatric disorders		
Very common	Insomnia	
Common	Depression, anxiety	
Uncommon		Insomnia, depression, anxiety
Eye disorders		
Common	Ocular hyperaemia	
Cardiac disorders		
Common	Atrial fibrillation, cardiac failure	Atrial fibrillation, cardiac failure,
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, colitis, haemorrhoids	Diarrhoea, colitis
Uncommon		Constipation, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common	Alopecia, pruritus	
Common	Night sweats, eczema	
Uncommon		Pruritus, night sweats

Frequency	All Grades Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)	Grades 3-5 [†] Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)
Musculoskeletal and connective tissue disorders		
Very common	Arthralgia [§] , back pain	
Common	Musculoskeletal chest pain, pain in extremity, 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	
Common	Chest pain	Pyrexia, asthenia
Uncommon		Chest pain
Investigations		
Common	White blood cell count decreased, neutrophil count decreased, weight increased	White blood cell count decreased, neutrophil count decreased
Injury, poisoning and procedural complications		
Very common	IRRs	IRRs

[#]with a higher incidence (difference of $\geq 2\%$ 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 $\geq 2\%$ 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 Gazyvaro 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 Gazyvaro plus bendamustine arm continued with Gazyvaro maintenance treatment.

During the maintenance period in study GAO4753g/GADOLIN, the most common adverse reactions were cough (15%), upper respiratory infections (12%), neutropenia (11%), sinusitis (10%), diarrhoea (8%), IRRs (8%), nausea (8%), fatigue (8%), bronchitis (7%), arthralgia (7%), pyrexia (6%), nasopharyngitis (6%), and urinary tract infections (6%). The most common Grade 3-5 adverse reactions were neutropenia (10%), and anaemia, febrile neutropenia, thrombocytopenia, 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.

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).

Infusion related reactions

Most frequently reported ($\geq 5\%$) 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 Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm. The incidence of IRRs was 65% with the infusion of the first 1,000 mg of Gazyvaro (20% of patients experiencing a Grade 3-4 IRR). Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyvaro. The incidence of IRRs with subsequent infusions was 3% with the second 1,000 mg dose and 1% thereafter. No Grade 3-5 IRRs were reported beyond the first 1,000 mg infusions of Cycle 1.

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 Gazyvaro plus chemotherapy compared to patients in the comparator arm. In patients receiving Gazyvaro 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 Gazyvaro alone. Beyond Cycle 1 the incidence of IRRs in subsequent infusions was comparable between the Gazyvaro and the relevant comparator arms. Overall, 3% of patients experienced an infusion related reaction leading to discontinuation of Gazyvaro.

Neutropenia and infections

Chronic Lymphocytic Leukaemia

The incidence of neutropenia was higher in the Gazyvaro 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 Gazyvaro plus chlorambucil arm and 37% in the rituximab plus chlorambucil arm (with Grade 3-5 events reported in 12% and 14%, respectively and fatal events reported in < 1% in both treatment arms). Cases of prolonged neutropenia (2% in the Gazyvaro plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the Gazyvaro plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported (see section 4.4).

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

In the Gazyvaro 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 7%, respectively. The incidence of infection was 81% in the Gazyvaro 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

Chronic Lymphocytic Leukaemia

The incidence of thrombocytopenia was higher in the Gazyvaro plus chlorambucil arm (15%) compared to the rituximab plus chlorambucil arm especially during the first cycle. Four percent of patients treated with Gazyvaro plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the Gazyvaro infusion) (see section 4.4). The overall incidence of haemorrhagic events was similar in the Gazyvaro treated arm and in the rituximab treated arm. The number of fatal haemorrhagic events was balanced between the treatment arms; however, all of the events in patients treated with Gazyvaro were reported in Cycle 1. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma

The incidence of thrombocytopenia was 14%. Thrombocytopenia occurred more frequently in Cycle 1 in the Gazyvaro plus chemotherapy arm. Thrombocytopenia occurring during or 24 hours from end of

infusion (acute thrombocytopenia) was more frequently observed in patients in the Gazyvaro 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 5% 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 Gazyvaro 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 Gazyvaro plus chlorambucil had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than patients with a CrCl \geq 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 8% (15 out of 194) of patients treated with Gazyvaro, respectively, had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events, adverse events leading to death and adverse events leading to treatment withdrawal than patients with a CrCl \geq 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

Progressive multifocal leukoencephalopathy

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

Hepatitis B reactivation

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

Gastro-Intestinal Perforation

Cases of gastro-intestinal perforation have been reported in patients receiving Gazyvaro, 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 arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyvaro (see section 4.4). These events may occur as part of an IRR and can be fatal.

Laboratory abnormalities

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

Reporting of suspected adverse reactions

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

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of obinutuzumab results in higher affinity for Fc γ RIII 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 Fc γ RIII 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 BO21004/CLL11, 91% (40 out of 44) of evaluable patients treated with Gazyvaro were B-cell depleted (defined as CD19+ B-cell counts $< 0.07 \times 10^9/L$) 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.

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 Gazyvaro plus chlorambucil (GC1b) compared to rituximab plus chlorambucil (RC1b) or chlorambucil (C1b) alone was conducted in patients with previously untreated chronic lymphocytic leukaemia with comorbidities.

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

A total of 781 patients were randomised 2:2:1 to receive Gazyvaro plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1a compared Gazyvaro plus chlorambucil to chlorambucil alone in 356 patients and Stage 2 compared Gazyvaro plus chlorambucil to rituximab plus chlorambucil in 663 patients. Efficacy results are summarised in Table 7 and in Figures 1-3.

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

The demographics data and baseline characteristics were well balanced between the treatment 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%).

Table 7 Summary of efficacy from BO21004/CLL11 study

	Stage 1a		Stage 2	
	Chlorambucil N=118	Gazyvaro + chlorambucil N= 238	Rituximab + chlorambucil N= 330	Gazyvaro + chlorambucil N= 333
	22.8 months median observation time		18.7 months median observation time	
Primary endpoint				
Investigator-assessed PFS (PFS-INV)^a				
Number (%) of patients with event	96 (81.4%)	93 (39.1%)	199 (60.3%)	104 (31.2%)
Median 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	Gazyvaro + chlorambucil N= 238	Rituximab + chlorambucil N= 330	Gazyvaro + chlorambucil N= 333
	22.8 months median observation time		18.7 months median observation time	
<i>Time to new anti-leukaemic therapy</i>				
No. (%) of patients with event	65 (55.1%)	51 (21.4%)	86 (26.1%)	55 (16.5%)
Median time to event (months)	14.8	-	30.8	-
Hazard ratio (95% CI)	0.24 [0.16; 0.35]		0.59 [0.42; 0.82]	
p-value (Log-Rank test, stratified ^b)	< 0.0001		< 0.0018	
<i>Overall survival</i>				
No. (%) of patients with event	24 (20.3%)	22 (9.2%)	41 (12.4%)	28 (8.4%)
Median time to event (months)	NR	NR	NR**	NR**
Hazard ratio (95% CI)	0.41 [0.23; 0.74]		0.66 [0.41; 1.06] **	
p-value (Log-Rank test, stratified ^b)	0.0022		0.0849**	

IRC: Independent Review Committee; PFS: progression-free survival; HR: Hazard Ratio; CI: Confidence Intervals, MRD: Minimal Residual Disease

^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

NR = Not reached

** Data not yet mature

Overall survival (OS) for Stage 1a is presented in Figure 2. OS for Stage 2 will continue to be followed and is not yet mature. 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)

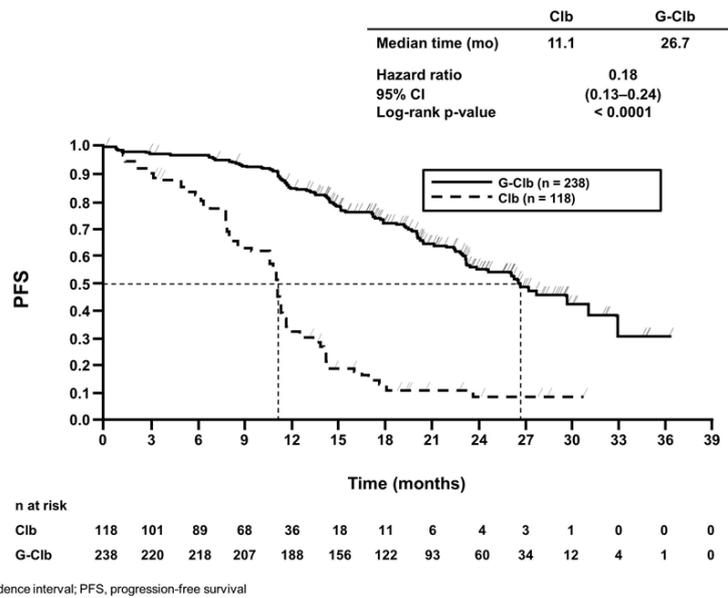


Figure 2 Kaplan-Meier curve of OS from Stage 1a in patients with CLL (Study BO21004/CLL11)

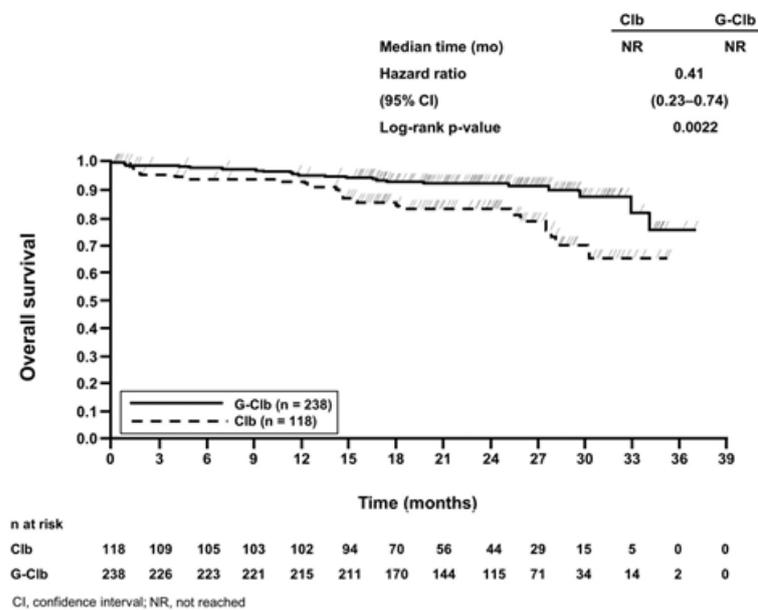
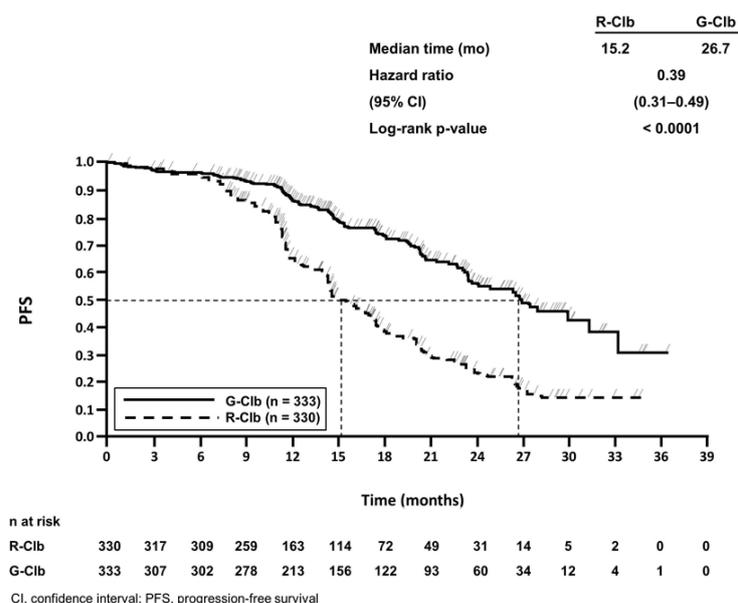


Figure 3 Kaplan-Meier curve of investigator assessed PFS from Stage 2 in patients with CLL (Study BO21004/CLL11)



Quality of life

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

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

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 Gazyvaro (n=601 patients) or rituximab (n=601 patients) in combination with chemotherapy (bendamustine, CHOP or CVP), followed by Gazyvaro or rituximab maintenance in patients achieving a complete or partial response.

Gazyvaro 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 Gazyvaro (every 28 days) were given in combination with six cycles of bendamustine, and a total of eight cycles of Gazyvaro (every 21 days) were given in combination with six cycles of CHOP or eight cycles of CVP. Gazyvaro was administered prior to chemotherapy. Bendamustine was given intravenously on Days 1 and 2 for all treatment cycles (Cycles 1-6) at 90 mg/m²/day when given in combination with Gazyvaro. Standard dosing of CHOP and CVP was given. Following Cycles 6-8, in combination with chemotherapy, responding patients received Gazyvaro 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 8. Kaplan-Meier curves for progression-free survival (PFS) are shown in Figure 4.

Table 8 Summary of efficacy in patients with previously untreated FL from BO21223/GALLIUM study

	Rituximab + Chemotherapy followed by rituximab maintenance N=601	Gazyvaro +Chemotherapy followed by Gazyvaro 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	
3 year PFS estimate [95% CI]	73.3 [68.8, 77.2]	80.0 [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	
Time to next anti-lymphoma therapy[#]		
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[#]		
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 [†]	

	Rituximab + Chemotherapy followed by rituximab maintenance N=601	Gazyvaro +Chemotherapy followed by Gazyvaro maintenance N=601
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%)
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: 0.012

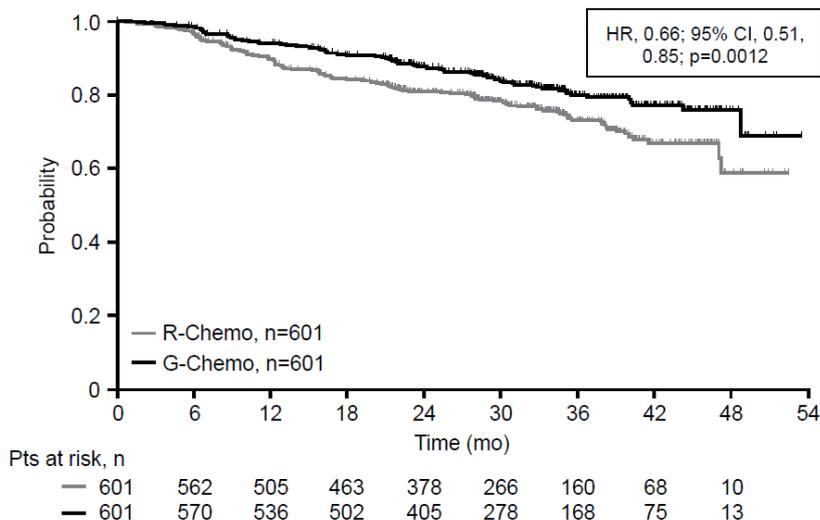
¶ Data Not Yet Mature. Median was not reached at time of analysis

not adjusted for multiplicity

**Assessed as per modified Cheson 2007 criteria

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

Figure 4 Kaplan-Meier curve of INV-assessed progression-free survival in patients with previously untreated FL (Study BO21223/GALLIUM)



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

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. 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 Gazyvaro 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 Gazyvaro 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 Gazyvaro 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 Gazyvaro 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.

Gazyvaro 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/m²/day when given in combination with Gazyvaro or 120 mg/m²/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 Gazyvaro 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 in the FL population are shown in Table 9. 11.6% of the patients had marginal zone lymphoma (MZL) and 7.1% had small lymphocytic lymphoma (SLL).

Table 9 Summary of efficacy in patients with FL# from GAO4753g/GADOLIN study

	Bendamustine N=166	Gazyvaro + Bendamustine followed by Gazyvaro 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	Gazyvaro + Bendamustine followed by Gazyvaro maintenance N=155
	Median observation time: 20 months	Median observation time: 22 months
Overall Survival (not yet mature)		
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

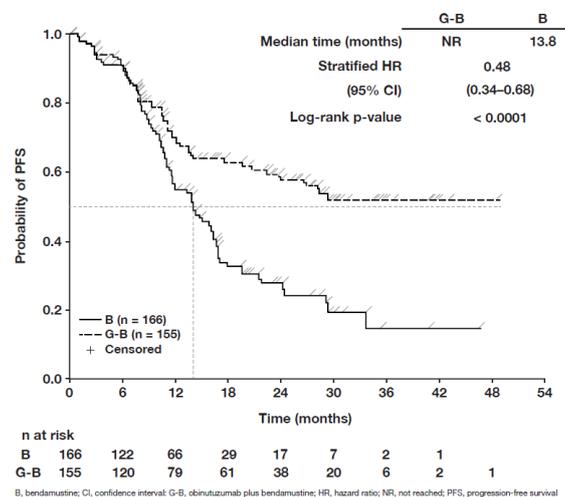
*Stratification factors for analysis were refractory type (rituximab monotherapy vs. rituximab + chemotherapy) and prior therapies (≤ 2 vs > 2). Follicular versus non-follicular was also a stratification factor for the study but is not applicable in the subgroup analysis of patients with FL.

§ Best response within 12 months of start of treatment

In the non-FL population the HR for IRC-assessed PFS was 0.94 [95% CI: 0.49, 1.90].

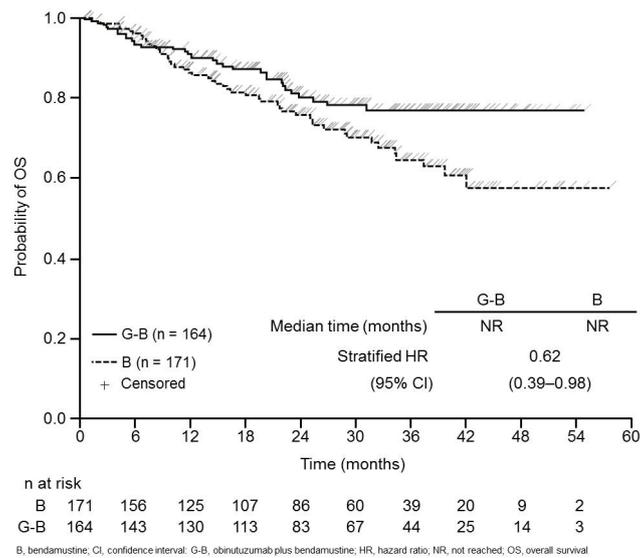
No definitive conclusions could be drawn on efficacy in the MZL and SLL sub-populations.

Figure 5 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 6 Kaplan-Meier curve of OS in patients with FL # (Study GAO4753g/GADOLIN)



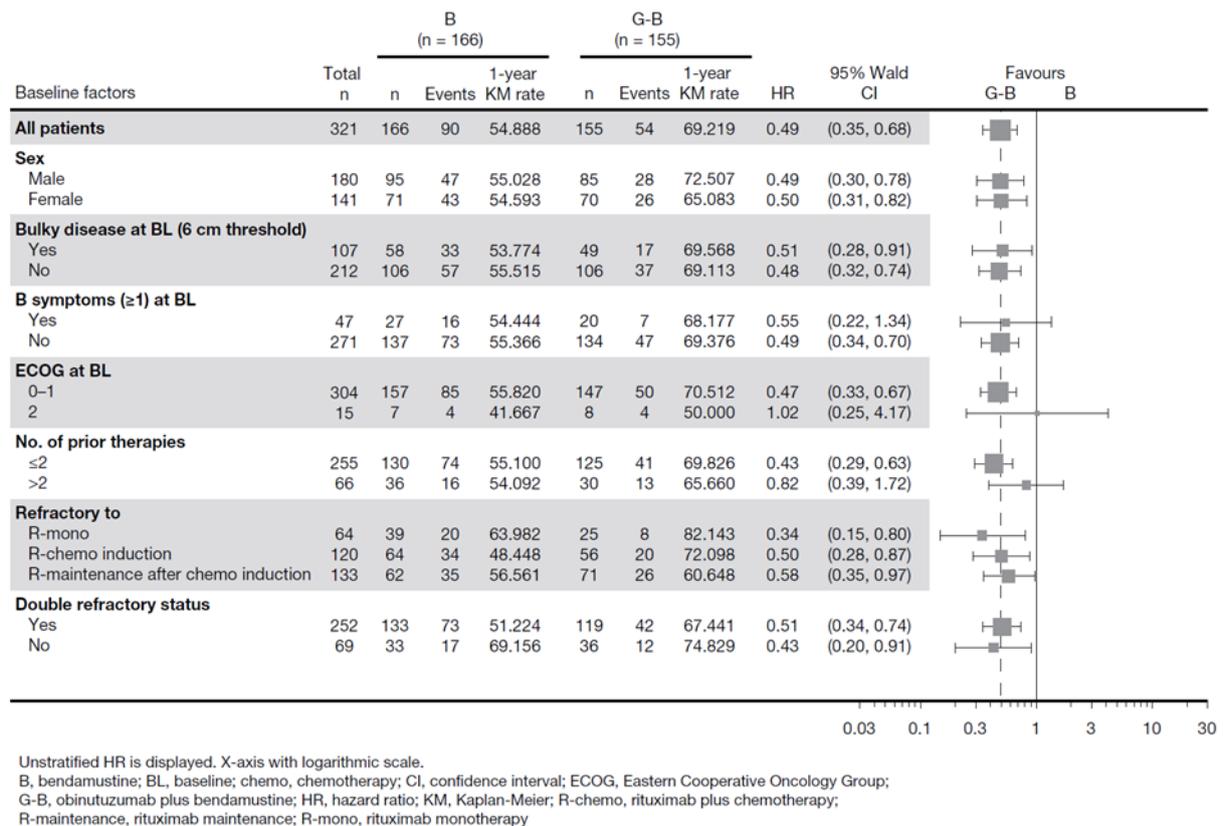
Patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

A post hoc analysis was performed 8 months after the primary analysis data cut. With a median observation time of 24.1 months for FL patients, 48 patients (28.1%) in the B arm and 30 patients (18.3%) in the G+B arm had died. The observed improvement in OS seen with G+B was supported by a stratified HR for OS of 0.62 (95% CI: 0.39, 0.98) in this post hoc analysis. The median OS was not yet reached for either arm. The PFS results in the post hoc analysis are consistent with the primary analysis and its significance is unchanged and the safety profile is consistent with the primary analysis.

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



*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

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 Gazyvaro 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 Gazyvaro/antibody in the circulation, sample handling, timing of sample collection, concomitant medicines and underlying disease. For these reasons, comparison of incidence of antibodies to Gazyvaro with the incidence of antibodies to other products may be misleading.

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

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.

Paediatric population

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

5.2 Pharmacokinetic properties

A population pharmacokinetic (PK) model was developed to analyse the PK data in 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 $\mu\text{g/mL}$ and $\text{AUC}(\tau)$ value was 8961 $\mu\text{g}\cdot\text{d/mL}$ and in iNHL patients the estimated median C_{max} value was 539.3 $\mu\text{g/mL}$ and $\text{AUC}(\tau)$ value was 10956 $\mu\text{g}\cdot\text{day/mL}$.

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 $t_{1/2}$ 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 (CL_{ss}) 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 $\mu\text{g}\cdot\text{d/mL}$ and 578.9 $\mu\text{g/mL}$ in females and 8451 $\mu\text{g}\cdot\text{d/mL}$ and 432.5 $\mu\text{g/mL}$ in males,

respectively at Cycle 6 and AUC and C_{\max} in iNHL of 13172 $\mu\text{g}\cdot\text{d}/\text{mL}$ and 635.7 $\mu\text{g}/\text{mL}$ in females and 9769 $\mu\text{g}\cdot\text{d}/\text{mL}$ and 481.3 $\mu\text{g}/\text{mL}$ 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 \geq 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

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years.

After dilution

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

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

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

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

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

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Instructions for dilution

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

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 Gazyvaro to be administered	Required amount of Gazyvaro concentrate	Size of PVC or non-PVC polyolefin infusion bag
100 mg	4 mL	100 mL
900 mg	36 mL	250 mL
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 Gazyvaro, in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of Gazyvaro with sodium chloride 9 mg/mL (0.9%) solution for injection, and:

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

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/937/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 July 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

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

Name and address of the manufacturer of the biological active substance

Roche Diagnostics GmbH
Nonnenwald 2
82377 Penzberg
GERMANY

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

• **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Gazyvaro 1,000 mg concentrate for solution for infusion
Obinutuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/937/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

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

2. METHOD OF ADMINISTRATION

For intravenous use after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1,000 mg/40 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Gazyvaro 1,000 mg concentrate for solution for infusion Obinutuzumab

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Gazyvaro is and what it is used for

What Gazyvaro is

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

What Gazyvaro is used for

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

- **Chronic lymphocytic leukaemia** (also called “CLL”)
 - Gazyvaro is used in patients who have not had any treatment for CLL before and who have other illnesses which make it unlikely that they would be able to tolerate a full dose of a different medicine used to treat CLL called fludarabine.
 - Gazyvaro is used together with another medicine for cancer called chlorambucil.
- **Follicular lymphoma** (also called “FL”)
 - Gazyvaro is used in patients who have not had any treatment for FL
 - Gazyvaro is used in patients who have had at least one treatment with a medicine called rituximab before and whose FL has come back or got worse during or after this treatment.
 - At the start of treatment for FL, Gazyvaro is used together with other medicines for cancer.
 - Gazyvaro can then be used on its own for up to 2 years as a “maintenance treatment”.

How Gazyvaro works

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

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

You must not be given Gazyvaro if:

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

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

Warnings and precautions

Talk to your doctor or nurse before you are given Gazyvaro if:

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

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

Pay attention to the following side effects

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

Infusion related reactions

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

Progressive multifocal leukoencephalopathy (also called “PML”)

- PML is a very rare and life-threatening brain infection that has been reported in very few patients having treatment with Gazyvaro.
- Tell your doctor or nurse straight away if you have memory loss, trouble speaking, difficulty walking or problems with your eyesight.
- If you had any of these symptoms before treatment with Gazyvaro, tell your doctor straight away if you notice any changes in them. You may need medical treatment.

Infections

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

Children and adolescents

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

Other medicines and Gazyvaro

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

Pregnancy

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

Breast-feeding

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

Contraception

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

Driving and using machines

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

3. How Gazyvaro is given

How Gazyvaro is given

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

The Gazyvaro treatment

Chronic lymphocytic leukaemia

- You will be given 6 treatment cycles of Gazyvaro in combination with another medicine for cancer called chlorambucil. Each cycle lasts 28 days.
- On Day 1 of your first cycle, you will be given part of your first Gazyvaro dose of 100 milligrams (mg) very slowly. Your doctor/nurse will monitor you carefully for infusion related reactions.
- If you do not have an infusion related reaction following the small part of your first dose, you may be given the rest of your first dose (900 mg) on the same day.
- If you do have an infusion related reaction following the small part of your first dose, you will be given the rest of your first dose on Day 2.

A typical schedule is shown below.

Cycle 1 - this will include three doses of Gazyvaro in the 28 days:

- Day 1 – part of your first dose (100 mg)
- Day 2 or Day 1 (continued) – remainder of first dose 900 mg
- Day 8 – full dose (1,000 mg)
- Day 15 – full dose (1,000 mg)

Cycles 2, 3, 4, 5 and 6 this will be just one dose of Gazyvaro in the 28 days:

- Day 1 – full dose (1,000 mg).

Follicular lymphoma

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

Induction phase

Cycle 1 - this will include three doses of Gazyvaro in the 28 or 21 days depending on which other cancer medicines are given together with Gazyvaro:

- Day 1 - full dose (1,000 mg)
- Day 8 - full dose (1,000 mg)
- Day 15 - full dose (1,000 mg).

Cycles 2-6 or 2-8 - this will be just one dose of Gazyvaro in the 28 or 21 days depending on which other cancer medicines are given together with Gazyvaro:

- Day 1 - full dose (1,000 mg).

Maintenance phase

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

Medicines given before each infusion

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

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

If you miss a Gazyvaro treatment

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

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

4. Possible side effects

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

Serious side effects

Infusion related reactions

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

Most frequently reported:

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

Less frequently reported:

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

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

Progressive multifocal leukoencephalopathy

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

Tell your doctor or nurse straight away if you have

- memory loss
- trouble speaking
- difficulty walking
- problems with your eyesight

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

Infections

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

Tell your doctor or nurse straight away if you get any signs of infection during and after your Gazyvaro treatment. These include:

- fever
- cough
- chest pain
- fatigue
- painful rash
- sore throat
- burning pain when passing urine
- feeling weak or generally unwell

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

Other side effects:

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

Very common (may affect more than 1 in 10 people)

- fever
- lung infection
- headache
- joint pain, back pain
- feeling weak
- diarrhoea, constipation
- sleeplessness
- hair loss, itchiness
- urinary tract infection, nose and throat inflammation, shingles

- changes in blood tests:
 - anaemia (low levels of red blood cells)
 - low levels of all types of white blood cell (combined)
 - low levels of neutrophils (a type of white blood cell)
 - low level of platelets (a type of blood cell that helps your blood to clot)

- infection of upper airways (infection of nose, pharynx, larynx and sinuses), cough

Common (may affect up to 1 in 10 people)

- red eye
- cold sores
- depression, anxiety
- night sweats
- flu (influenza)
- weight increase
- lymph node pain
- runny or blocked nose
- eczema
- nose or throat inflammation
- pain in mouth or throat
- muscle and bone pain in your chest
- skin cancer (squamous cell carcinoma)
- bone pain, pain in arms and legs
- irregular heart beat (atrial fibrillation), heart attack
- problems with urinating, urinary incontinence
- problems with digestion (e.g. heartburn), inflammation of the intestine, haemorrhoids
- changes shown in blood tests:
 - low levels of lymphocytes (a type of white blood cells)
 - increase in potassium, phosphate or uric acid - which can cause kidney problems (part of tumour lysis syndrome)
 - decrease in potassium

Uncommon (may affect up to 1 in 100 people)

- a hole in the stomach or intestines (gastrointestinal perforation, especially in cases where the cancer affects the gastrointestinal tubes)

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

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Gazyvaro

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

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

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

6. Contents of the pack and other information

What Gazyvaro contains

- The active substance is obinutuzumab: 1,000 mg/40 mL per vial corresponding to a concentration before dilution of 25 mg/mL.
- The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, trehalose dihydrate, poloxamer 188 and water for injections.

What Gazyvaro looks like and contents of the pack

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

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Manufacturer

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This leaflet was last revised in

Other sources of information

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

The following information is intended for healthcare professionals only:

Posology

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

Prophylaxis and premedication for tumour lysis syndrome (TLS)

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

Prophylaxis and premedication for infusion related reactions (IRRs)

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

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

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

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

¹100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

² e.g. 1,000 mg acetaminophen/paracetamol

³ e.g. 50 mg diphenhydramine

⁴ If a corticosteroid-containing chemotherapy regimen is administered on the same day as Gazyvaro, the corticosteroid can be administered as an oral medication if given at least 60 minutes prior to Gazyvaro, in which case additional IV corticosteroid as premedication is not required.

Dose

Chronic lymphocytic leukaemia (in combination with chlorambucil¹)

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

Cycle 1

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

Cycles 2 - 6

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

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

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

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

Duration of treatment

Six treatment cycles, each of 28 day duration.

Follicular lymphoma

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

Patients with previously untreated follicular lymphoma

Induction (in combination with chemotherapy²)

Gazyvaro should be administered with chemotherapy as follows:

- Six 28-day cycles in combination with bendamustine² or
- Six 21-day cycles in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP), followed by 2 additional cycles of Gazyvaro alone or
- Eight 21-day cycles in combination with cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone (CVP).

Maintenance

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

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

Induction (in combination with bendamustine²)

Gazyvaro should be administered in six 28-day cycles in combination with bendamustine².

Maintenance

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

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

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

² Bendamustine is given intravenously on Days 1 and 2 of all treatment cycles (Cycles 1-6) at 90 mg/m²/day; CHOP and CVP according to standard regimens

Duration of treatment

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

Method of administration

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

For instructions on dilution of Gazyvaro before administration, see below. Instructions on the rate of infusion are shown in Tables 4 and 5.

Chronic Lymphocytic Leukaemia

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

Cycle	Day of treatment	Rate of infusion The infusion rate may be escalated provided that the patient can tolerate it. For management IRRs that occur during the infusion, refer to “Management of IRRs”.
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 occurred during the previous infusion, administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. If the patient experienced an IRR during the previous infusion, start with administration at 25 mg/hr. The rate of infusion can be escalated in increments up to 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8 (1,000 mg)	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.
	Day 15 (1,000 mg)	
Cycles 2-6	Day 1 (1,000 mg)	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.

Follicular lymphoma (FL)

Table 5 Follicular lymphoma: Standard infusion rate in the absence of IRR/hypersensitivity and recommendations in case an IRR occurred with previous infusion

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

Management of IRRs (all indications)

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

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 4 and 5). 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 and 5). 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.

Instructions for dilution

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

For CLL cycles 2 – 6 and all FL cycles

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

CLL only – Cycle 1

To ensure differentiation of the two infusion bags for the initial 1,000 mg dose, it is recommended to utilise bags of different sizes to distinguish between the 100 mg dose for Cycle 1 Day 1 and the 900 mg dose for Cycle 1 Day 1 (continued) or Day 2. To prepare the 2 infusion bags, withdraw 40 mL of concentrate from the vial and dilute 4 mL into a 100 mL PVC or non-PVC polyolefin infusion bag and the remaining 36 mL in a 250 mL PVC or non-PVC polyolefin infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection. Clearly label each infusion bag.

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

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

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

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

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

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

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

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

Disposal

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

ANNEX IV

**CONCLUSIONS ON THE REQUEST FOR ONE-YEAR MARKETING PROTECTION
PRESENTED BY THE EUROPEAN MEDICINES AGENCY**

Conclusions presented by the European Medicines Agency on:

- **one-year marketing protection**

The CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies as further explained in the European Public Assessment Report.