**Gazyvaro®**

Obinutuzumab

# Composition

## Active substances

Obinutuzumab (manufactured by recombinant DNA technology using CHO [Chinese hamster ovary] cells).

## Excipients

L-Histidine, L-histidine hydrochloride monohydrate, trehalose dihydrate, poloxamer 188, water for injection.

# Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.

Each 40 ml vial contains 1000 mg obinutuzumab.

## Indications/UsesChronic lymphocytic leukaemia

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

## Follicular lymphoma

Gazyvaro in combination with chemotherapy followed by subsequent maintenance therapy (for a maximum of 2 years) is indicated for the treatment of patients with previously untreated follicular lymphoma (FL) who require systemic therapy. For therapeutic indication, see “Clinical efficacy”, and for the duration of induction and maintenance therapy, see “Dosage/Administration”.

Gazyvaro in combination with bendamustine, followed by Gazyvaro maintenance therapy (for a maximum of 2 years), is indicated for the treatment of patients with follicular lymphoma (FL) who have not responded to therapy or have progressed during or after treatment with rituximab or a rituximab-containing regimen.

For the duration of induction and maintenance therapy, see “Dosage/Administration”.

# Dosage/Administration

Treatment with Gazyvaro should only be conducted under the supervision of a medical specialist experienced in the management of cancer patients. The infusion should only be administered in a place where full resuscitation facilities are immediately available and under the close supervision of an experienced physician.

To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

## Prophylaxis and premedication for tumour lysis syndrome (TLS)

Patients with a high tumour burden and/or a high circulating lymphocyte count (>25 × 109/l) and/or renal impairment (CrCl <70 ml/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should be given according to institutional practice before the start of Gazyvaro infusion and consist of adequate hydration and administration of uricostatics (e.g. allopurinol) or a suitable alternative such as urate oxidase (e.g. rasburicase) (see “Warnings and precautions”). Patients should also receive prophylaxis before each subsequent infusion, if deemed appropriate.

## Prophylaxis and premedication for infusion reactions (IRRs)

To prevent infusion reactions, premedication with an analgesic/antipyretic (e.g. paracetamol) and an antihistamine (e.g. diphenhydramine) should be given 30 to 60 minutes before every Gazyvaro infusion.

Premedication with a corticosteroid is recommended before the first infusion in FL patients. Such premedication is mandatory in CLL patients.

Intravenous glucocorticoids (100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone; hydrocortisone is not recommended in CLL as it has not been effective in reducing the rate of infusion reactions) should be given at least one hour before the start of the Gazyvaro infusion to all patients in the first cycle (CLL: days 1 and 2, FL: day 1) and, in subsequent cycles, to those who have experienced a grade 3 infusion reaction during the previous infusion or with a lymphocyte count >25 × 109/l prior to the next treatment. If corticosteroid-containing chemotherapy is administered on the same day as Gazyvaro, the corticosteroid may be administered orally if given at least 60 minutes before Gazyvaro. In the event of oral corticosteroid administration, additional premedication with an intravenous corticosteroid is not required.

Hypotension may occur as a feature of infusion reactions during Gazyvaro intravenous infusions. Therefore, interruption of antihypertensive treatments should be considered for 12 hours before, during and for the first hour after each Gazyvaro infusion.

###### Chronic lymphocytic leukaemia

Gazyvaro is administered as an intravenous infusion through a dedicated line and must not be given as an intravenous push or bolus infusion. Isotonic 0.9% sodium chloride solution should be used to prepare the infusion solution. At the start of treatment (first infusion) the total dose should be distributed to two infusion bags (bag 1 with 100 mg and bag 2 with 900 mg) (see “Other information, Instructions for handling and disposal”).

The recommended dosage of obinutuzumab is 1000 mg administered 3 times in the first cycle and once in each of cycles 2-6 (28-day cycles).

First infusion: The first infusion is administered at a rate of 25 mg/h over 4 hours (bag 1 with 100 mg obinutuzumab). If no infusion reactions (IRRs) have occurred, the second bag (bag 2 with 900 mg obinutuzumab) can be infused immediately afterwards, starting at a rate of 50 mg/h, provided that sufficient time, appropriate conditions and medical supervision are available during the infusion. After the first 30 minutes the infusion rate can be escalated in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h. If an infusion reaction has occurred during the first 100 mg obinutuzumab (see Table 1 for procedure), the second bag must be administered the following day. If the patient has experienced an IRR during the previous infusion, administration is started at a rate of 25 mg/h. After the first 30 minutes the infusion rate can be escalated in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h. Patients developing respiratory symptoms or hypotension should be monitored for 24 hours.

Subsequent infusions (cycle 1 days 8 and 15 and cycles 2-6): If no IRRs have occurred during the previous infusion at a final infusion rate of ≥100 mg/h, subsequent infusions can be started at a rate of 100 mg/h and increased after the first 30 minutes by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h. If the patient has experienced an IRR during the previous infusion, start at a rate of 50 mg/h. After 30 minutes the infusion rate can be escalated in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h.

###### Follicular lymphoma

Gazyvaro is administered as an intravenous infusion through a dedicated line and must not be given as an intravenous push or bolus infusion. Isotonic 0.9% sodium chloride solution should be used to prepare the infusion solution.

***Previously untreated follicular lymphoma***

Induction therapy

The recommended dosage of obinutuzumab in combination with chemotherapy is 1000 mg (administered 3 times in the first cycle, days 1, 8 and 15):

* and once on day 1 in each of cycles 2‑6 (28-day cycles) in combination with bendamustine
* or once on day 1 in each of cycles 2‑6 (21-day cycles) in combination with CHOP, followed by 2 additional cycles of Gazyvaro alone or once on day 1 in each of cycles 2‑8 (21-day cycles) in combination with CVP.

Maintenance therapy

Previously untreated patients with complete or partial response to induction therapy (Gazyvaro plus chemotherapy) should continue on maintenance therapy with Gazyvaro (1000 mg obinutuzumab once every 2 months) until disease progression or for up to 2 years.

### *Relapsed/refractory follicular lymphoma*

In patients with follicular lymphoma who have relapsed after or who have failed to respond to treatment with rituximab or a rituximab-containing regimen, Gazyvaro should be administered in six 28-day cycles in combination with bendamustine. Relapsed/refractory patients who achieve complete or partial response or stable disease should continue on maintenance therapy of 1000 mg Gazyvaro once every 2 months until disease progression or for up to 2 years.

The recommended dosage of obinutuzumab is 1000 mg administered 3 times in the first cycle, days 1, 8 and 15, and once in each of cycles 2-6 (28-day cycles), followed by administration every 2 months (infusion of 1000 mg obinutuzumab on each occasion) until disease progression or for up to two years.

The recommended dosage of bendamustine in combination with obinutuzumab is 90 mg/m2, administered intravenously on days 1 and 2 in each of cycles 1-6 (28-day cycles).

###### All patients with follicular lymphoma

First infusion (cycle 1 day 1): The first infusion (1000 mg obinutuzumab) is started at a rate of 50 mg/h. After the first 30 minutes the infusion rate can be escalated in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h. Patients developing respiratory symptoms or hypotension should be monitored for 24 hours.

Subsequent infusions (each with 1000 mg obinutuzumab, cycle 1 days 8 and 15 and cycles 2‑6/8, followed by maintenance therapy with 1000 mg obinutuzumab every 2 months until disease progression or for up to two years):

If no IRRs or a grade 1 IRR has occurred during the previous infusion at a final infusion rate of ≥100 mg/h, subsequent infusions can be started at a rate of 100 mg/h and increased after the first 30 minutes by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h. If the patient has experienced an IRR of grade 2 or higher during the previous infusion, start at a rate of 50 mg/h. After 30 minutes the infusion rate can be escalated in increments of 50 mg/h every 30 minutes to a maximum of 400 mg/h.

Table 1: Infusion rate modification guidelines for infusion reactions (all indications)

|  |  |
| --- | --- |
| **Grade 4 (life-threatening)** | Stop infusion and permanently discontinue therapy. |
| **Grade 3 (severe)** | Temporarily interrupt infusion and treat symptoms.  Once symptoms resolve, the infusion can be resumed at no more than half the previous rate (at time of infusion reaction). If no more infusion reaction symptoms occur, infusion rate escalation may resume. If a second grade 3 infusion reaction occurs, treatment with Gazyvaro should be discontinued. In CLL patients in whom the first dose of cycle 1 is divided over two days, the infusion rate on day 1 can be increased back to 25 mg/h after 1 hour, but must not be increased further. |
| **Grades 1-2 (mild and moderate)** | Reduce infusion rate and treat symptoms.  Once symptoms resolve, continue infusion. If no further infusion reaction symptoms occur, the infusion rate may be escalated at the increments and intervals appropriate to the treatment dose (see “Subsequent infusions” above). In CLL patients in whom the first dose of cycle 1 is divided over two days, the infusion rate on day 1 can be increased back to 25 mg/h after 1 hour, but must not be increased further. |

## Delayed administration

If a planned dose of Gazyvaro is missed, it should be administered as soon as possible; do not omit the dose and do not wait until the next planned dose. If toxicity occurs before cycle 1 day 8 or cycle 1 day 15 that makes it necessary to postpone treatment, these doses should be given after resolution of toxicity. In such cases, all subsequent visits and the start of cycle 2 must be shifted to accommodate the delay in cycle 1. During maintenance therapy, keep to the original dosing schedule.

## Dosage modifications during treatment

Dose reduction of Gazyvaro is not recommended. For management of symptomatic adverse events (including IRRs), see “Warnings and precautions”.

For bendamustine dose adjustment, please consult the prescribing information for bendamustine.

## Special dosage instructions

Patients with impaired hepatic function

The safety and efficacy of Gazyvaro have not been studied in patients with hepatic impairment.

## *Patients with impaired renal function*

No dose adjustment is required in patients with mild or moderate renal impairment.

Gazyvaro has not been studied in patients with CrCl <30 ml/min (see “Undesirable effects” and “Pharmacokinetics”).

## Elderly *patients*

No dose adjustment is required in patients ≥65 years of age.

## Children *and adolescents*

No safety and efficacy studies have been conducted in children and adolescents under 18 years of age.

# Contraindications

Known hypersensitivity to the active substance or to any of the excipients.

# Warnings and precautions

#### Infusion reactions

The most frequently observed adverse drug reactions (ADRs) in patients receiving Gazyvaro were infusion reactions (IRRs), which occurred predominantly during infusion of the first 1000 mg. The measures for preventing infusion reactions described under “Dosage/Administration” decreased the incidence of all-grade infusion reactions in CLL patients. However, the incidences of grade 3‑4 infusion reactions were similarly frequent with and without these measures. The preventive measures to reduce IRRs (see “Dosage/Administration”) should be undertaken. Most patients had no infusion reactions during subsequent infusions of Gazyvaro.

In the majority of patients, regardless of indication, infusion reactions were mild to moderate and could be managed by slowing or temporarily halting the first infusion, but severe and life-threatening infusion reactions requiring symptomatic treatment have also been reported. CLL patients with a high tumour burden and/or a high number of circulating lymphocytes (>25 × 109/l) may be at increased risk of severe infusion reactions. See “Dosage/Administration” for information on prophylaxis and Infusion rate modification guidelines for infusion reactions in Table 1 on how to manage IRRs based on grade of reaction.

Patients experiencing any of the following events should not receive further Gazyvaro infusions:

* Acute life-threatening respiratory symptoms
* A grade 4 (i.e. life threatening) infusion reaction or
* A second (prolonged/recurrent) grade 3 infusion reaction (after resuming the first infusion or during a subsequent infusion).

Patients with pre-existing cardiac or pulmonary conditions should be carefully monitored during and after the infusion. Hypotension may be expected to occur during Gazyvaro infusions. Therefore, discontinuation of antihypertensive medications should be considered for 12 hours before, during and for the first hour after each Gazyvaro infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of discontinuing their antihypertensive medication.

#### Hypersensitivity reactions including anaphylaxis

Hypersensitivity reactions of the immediate type (e.g. anaphylaxis) or delayed type (e.g. serum sickness) have been reported in patients treated with Gazyvaro. If a hypersensitivity reaction is suspected during or after an infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped and treatment permanently discontinued. Patients with known hypersensitivity to Gazyvaro must not be treated with Gazyvaro (see “Contraindications”). Hypersensitivity reactions may be clinically difficult to distinguish from infusion reactions.

#### Tumour lysis syndrome.

Cases of tumour lysis syndrome (TLS) have been reported during treatment with Gazyvaro. Patients considered at risk of TLS (e.g. patients with a high tumour burden and/or a high circulating lymphocyte count [>25 × 109/l] and/or renal impairment [CrCl <70 ml/min]) should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol) or a suitable alternative such as urate oxidase (e.g. rasburicase) before the start of Gazyvaro infusion, as described under “Dosage/Administration”. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function and potassium and uric acid levels. All additional institutional practice guidelines should also be followed.

For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and initiate supportive measures, 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 laboratory tests until resolution. If treatment is necessary, it should be administered in accordance with local guidelines and administration of granulocyte colony-stimulating factors (G‑CSF) should be considered. Any signs of concomitant infection should be treated as appropriate. Late-onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) may occur.

#### Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with Gazyvaro.

Fatal haemorrhagic events have also occurred in cycle 1 during treatment with Gazyvaro.

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. The benefit-risk balance of any concomitant therapies that could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be carefully considered, 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 during treatment with Gazyvaro. These events may occur as part of an infusion reaction 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 potential fluid overload.

#### Infections

Gazyvaro should not be administered in the presence of an active infection. 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.

In the FL studies, a high incidence of infections was observed in every phase of treatment, including follow-up, with the highest incidence seen during maintenance therapy. In the follow-up phase, grade 3‑5 infections were observed more often in patients who had received Gazyvaro plus bendamustine in the induction phase.

Patients with severe viral infections should not be treated with Gazyvaro. Severe viral infections, both new and reactivated or exacerbated, have been reported on treatment with anti-CD20 antibodies and have been fatal in isolated cases. Examples of such severe viral infections include infections with herpesviruses (cytomegaly, herpes zoster, herpes simplex), JC virus (progressive multifocal leukoencephalopathy [PML]) and hepatitis B or hepatitis C virus.

#### 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 “Undesirable effects”). HBV screening should be performed in all patients before initiation of treatment with Gazyvaro. At minimum this should include determination of HBsAg and anti-HBc, which can be complemented with other markers. Patients with active hepatitis B should not be treated with Gazyvaro. Patients with positive hepatitis B serology should consult a hepatologist before starting treatment. HBV reactivation has been reported in hepatitis B surface antigen-positive (HBsAg-positive) patients, as well as in HBsAg-negative and anti-HBs-positive patients.

Patients with existing or previous HBV infection should be observed for clinical symptoms or laboratory findings indicative of hepatitis or HBV reactivation during and for at least 12 months after treatment with Gazyvaro. Gazyvaro must be discontinued immediately in the event of hepatitis B reactivation. Resumption of treatment should be discussed with a physician experienced in the treatment of hepatitis B. No data are available on the safety of treatment resumption with Gazyvaro in patients with reactivated hepatitis B.

#### Progressive multifocal leukoencephalopathy (PML)

Cases of PML have been reported. The diagnosis of PML should be considered in any patient with new-onset or changes to pre-existing neurological manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis and sensory disturbances), sensory abnormalities, cerebellar symptoms and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g. aphasia or visual-spatial disorientation) may also occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI) and lumbar puncture (CSF testing for JC viral DNA). Therapy with 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. Vaccination with live virus vaccines is not recommended during treatment and until B cell recovery.

#### Intrauterine exposure to Gazyvaro and vaccination of newborns with live virus vaccines

Due to the potential for B cell depletion in newborns whose mothers have been exposed to Gazyvaro during pregnancy, the safety and timing of vaccinations with live virus vaccines should be discussed with the paediatrician. In newborns of mothers exposed to Gazyvaro during pregnancy, consider postponing vaccinations with live virus vaccines until B cell counts are within the normal range.

# Interactions

No drug-drug interaction studies have been performed, although substudies have been undertaken to a limited extent on drug interactions between Gazyvaro and bendamustine and chlorambucil. Coadministration of Gazyvaro did not affect the pharmacokinetics of bendamustine. There were likewise no discernible effects of bendamustine or chlorambucil on Gazyvaro pharmacokinetics. A risk of interactions with concomitantly used medicinal products cannot be excluded.

# Pregnancy, lactation

## Pregnancy

Gazyvaro should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Women of childbearing potential should use a reliable method of contraception during treatment with Gazyvaro and for 18 months thereafter (see “Pharmacokinetics, Elimination”). In newborns of mothers exposed to Gazyvaro during pregnancy, consider postponing vaccinations with live virus vaccines until B cell counts are within the normal range.

No studies have been conducted in pregnant women. A reproduction study in cynomolgus monkeys produced no evidence of embryofetal toxicity or teratogenic effects, but showed complete depletion of B lymphocytes in the newborn. B cell counts in the newborn returned to normal levels and immunological function was restored within 6 months of birth (see “Preclinical data, Reproductive toxicity”). Furthermore, the serum concentrations of Gazyvaro in the newborn 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 Gazyvaro crosses the placenta.

## Lactation

Because human IgG is excreted in human milk, and the potential for absorption and harm to the newborn is unknown, women should be advised to discontinue nursing during Gazyvaro therapy and for 18 months after the last dose of Gazyvaro. Animal studies have shown excretion of Gazyvaro in the milk (see “Preclinical data, Reproductive toxicity”).

# Effects on ability to drive and use machines

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

# Undesirable effects

***Clinical studies*** Patients with various haematological disorders (e.g. CLL and iNHL) were treated in clinical trials with Gazyvaro, predominantly in combination with chemotherapy (CHOP, CVP, chlorambucil or bendamustine). The safety profile from the clinical trial population of approximately 4900 patients is presented in this section (see also “Properties/Effects, Clinical efficacy”).

The most serious adverse drug reactions were:

* Infusion reactions, predominantly in CLL patients (see “Warnings and precautions”)
* Tumour lysis syndrome, predominantly in patients with a high tumour burden and/or a high circulating lymphocyte count and/or renal impairment (see “Warnings and precautions”)
* Thrombocytopenia, which can be fatal in the first cycle (see “Warnings and precautions”)

The most frequently observed adverse drug reactions in patients receiving Gazyvaro in clinical trials were IRR, neutropenia, diarrhoea, constipation and cough.

Adverse drug reactions associated with the use of Gazyvaro in combination with different chemotherapy regimens in multiple indications are listed below. The listed adverse drug reactions fall into the categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000). The adverse drug reactions were assigned to the appropriate category according to the highest incidence seen in any of the major clinical trials.

#### Infections and infestations

*Very common*: Upper respiratory tract infection (all grades: 22.1%, grade 3‑5: 2.0%), sinusitis (all grades: 12.3%, grade 3‑5: 1.0%), herpes zoster (all grades: 11.0%, grade 3‑5: 1.6%), pneumonia (all grades: 10.9%, grade 3‑5: 5.4%), urinary tract infection (all grades 11.8%, grade 3‑5: 2.9%), nasopharyngitis (all grades 10.8%, grade 3-5 <1%).

*Common*: Oral herpes, rhinitis, pharyngitis, pulmonary infection, influenza.

*Isolated cases*: Progressive multifocal leukoencephalopathy (PML), reactivation of hepatitis B.

#### Benign, malignant and unspecified neoplasms (including cysts and polyps)

*Common*: Squamous cell carcinoma of skin, basal cell carcinoma.

#### Blood and lymphatic system disorders

*Very common*: Neutropenia (all grades: 50.7%, grade 3‑5: 46.8%), thrombocytopenia (all grades: 15.4%, grade 3‑5: 11.2%), anaemia all grades: 12.4% (grade 3‑5: 6.9%), leukopenia (all grades: 12.5%, grade 3‑5: 8.7%).

*Common*: Lymph node pain, neutrophil count decreased, white blood cell count decreased, febrile neutropenia.

#### Immune system disorders

*Isolated cases*: Anaphylaxis.

#### Metabolism and nutrition disorders

*Common*: Hypokalaemia, tumour lysis syndrome, hyperuricaemia.

#### Psychiatric disorders

*Very common*: Insomnia (all grades: 14.3%, grade 3‑5: <1%).

*Common*: Depression, anxiety.

#### Eye disorders

Common: Ocular hyperaemia\*.

#### Cardiac disorders

*Common*: Atrial fibrillation, heart failure\*.

#### Vascular disorders

*Common*: Hypertension.

#### Respiratory, thoracic and mediastinal disorders

*Very common*: Cough (all grades: 30.8%, grade 3‑5: <1%).

*Common*: Nasal congestion, rhinorrhoea, oropharyngeal pain.

#### Gastrointestinal disorders

*Very common*: Constipation (all grades: 32.4%, grade 3‑5: <1%), diarrhoea (all grades: 28.4%, grade 3‑5: 2.5%).

*Common*: Dyspepsia, colitis\*, haemorrhoids.

Uncommon: Transaminase elevation\*.

#### Skin and subcutaneous tissue disorders

*Very common*: Alopecia (all grades: 12.6%, grade 3‑5: 0%), pruritus (all grades 10.6%, grade 3‑5: <1%).

*Common*: Night sweats\*, eczema.

#### Musculoskeletal and connective tissue disorders

*Very common*: Arthralgia (all grades: 15.9%, grade 3‑5: <1%), back pain (all grades: 13.5%, grade 3‑5: <1%), pain in extremity (all grades: 10.3%, grade 3‑5: 1%).

*Common*: Musculoskeletal chest pain, bone pain.

#### Nervous system disorders

*Very common*: Headache (all grades: 16.8%, grade 3‑5: <1%).

#### Renal and urinary disorders

*Common*: Dysuria, urinary incontinence.

#### General disorders and administration site conditions

*Very common*: Pyrexia (all grades: 20.3%, grade 3‑5: 2.4%), infusion reactions (all grades: 71.6%, grade 3‑5: 21.2%), asthenia (all grades: 11.8%, grade 3‑5: 1.0%), fatigue (all grades 34.0%, grade 3‑5: 2.5%).

*Common*: Chest pain.

#### Investigations

*Common*: Weight increased.

\*In the primary analysis of study GAO4753g/GO01297 the incidence versus the comparator was ≥2%, but was <2% in the final analysis.

###### Maintenance therapy in iNHL patients

In study GAO4753g, patients in the bendamustine arm received 6 months of induction treatment only, whereas after the induction period, patients in the Gazyvaro plus bendamustine arm received maintenance treatment with Gazyvaro. During the maintenance period with Gazyvaro, the most common adverse reactions were cough (20.3%), neutropenia (12.7%), upper respiratory tract infections (12.0%), diarrhoea (10.1%), bronchitis (9.5%), sinusitis (9.5%), nausea (8.9%), fatigue (8.9%), infusion reactions (8.2%), urinary tract infections (7.0%), nasopharyngitis (7.0%), pyrexia (7.0%), arthralgia (6.3%), vomiting (5.7%), rash (5.7%), pneumonia (5.1%), dyspnoea (5.1%) and pain in extremity (5.1%).

The most common grade 3‑5 adverse reactions observed during the maintenance period were neutropenia (10.8%), febrile neutropenia (1.9%), anaemia, thrombocytopenia, pneumonia, sepsis, upper respiratory tract infection and urinary tract infection (each 1.34 %).

#### Further information on selected adverse drug reactions

Infusion reactions (IRRs)

The symptoms reported most frequently (≥5%) in association 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 “Warnings and precautions”).

## Chronic lymphocytic leukaemia

The incidence of IRRs was 65% with the infusion of the first 1000 mg of Gazyvaro (20% of patients experiencing a grade 3-4 IRR, with no fatal events reported). No grade 3‑4 IRRs were reported on infusion of the second 1000 mg or thereafter. Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyvaro. The incidence of IRRs was 3% on infusion of the second 1000 mg dose and 1% with the third and subsequent infusions. In patients who received the recommended measures for prevention of IRRs as described under “Dosage/Administration”, a trend towards decreased incidence of all-grade IRRs was observed. These measures did not appear to reduce the incidence of grade 3‑4 IRRs.

## Non-Hodgkin’s lymphoma (mainly FL)

In cycle 1, the overall incidence of IRRs in patients treated with Gazyvaro plus chemotherapy was higher than that for patients in the comparator arm. In patients treated with Gazyvaro plus chemotherapy, the IRR incidence was highest on day 1 and gradually decreased with subsequent infusions. This downward trend continued during maintenance therapy with Gazyvaro. Overall, 40% of patients experienced an IRR leading to discontinuation of Gazyvaro.

## *Neutropenia and infections*

Chronic lymphocytic leukaemia

The incidence of infections in the Gazyvaro plus chlorambucil arm was 38%, with grade 3‑5 events reported in 12% and fatal events in <1%. There were also reports of prolonged neutropenia in 2% of patients and late-onset neutropenia in 16% (see “Warnings and precautions”).

## Non-Hodgkin’s lymphoma (mainly FL)

In the Gazyvaro plus chemotherapy arm, the incidence of neutropenia was higher than in the comparator arm, with an increased risk during the induction phase. The incidences of prolonged neutropenia and late-onset neutropenia in the Gazyvaro plus chemotherapy arm were 3% and 7%, respectively. The incidence of infections in the Gazyvaro plus chemotherapy arm was 81% (with 22% grade 3‑5 events and 3% fatal events). Patients who received G‑CSF prophylaxis had a lower rate of grade 3‑5 infections.

## *Thrombocytopenia and* haemorrhagic *events*

Chronic lymphocytic leukaemia

Four percent of patients treated with Gazyvaro plus chlorambucil experienced acute thrombocytopenia (starting within 24 hours of Gazyvaro infusion) (see “Warnings and precautions”). A clear relationship was not demonstrated between the thrombocytopenia and bleeding events.

## Non-Hodgkin’s lymphoma (mainly FL)

During cycle 1, thrombocytopenia occurred more frequently in the Gazyvaro plus chemotherapy arm. Thrombocytopenia occurring during or within 24 hours of infusion (acute thrombocytopenia) was more frequent in patients treated with Gazyvaro plus chemotherapy than in the relevant comparator arm. Haemorrhagic events and grade 3‑5 haemorrhagic events occurred in 12% and 5% of patients, respectively. Less than 1% of patients experienced fatal haemorrhagic events, and none of these fatal AEs occurred in cycle 1.

## *Progressive multifocal leukoencephalopathy (PML)*

Cases of PML have been reported in patients treated with Gazyvaro (see “Warnings and precautions”).

## *Hepatitis B reactivation*

Cases of hepatitis B reactivation have been reported in patients treated with Gazyvaro (see “Warnings and precautions”).

## *Worsening of pre-existing cardiac conditions*

Cases of fatal cardiac events have been reported in patients treated with Gazyvaro (see “Warnings and precautions”).

## *Gastrointestinal perforation*

Cases of gastrointestinal perforation have been reported in patients receiving Gazyvaro, primarily NHL patients.

## *Renal impairment*

In patients with moderate renal impairment (CrCl <50 ml/min), more serious adverse events (grade 3 to 5)41 occurred than in those with creatinine clearance (CrCl) ≥50 ml/min.

Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

**Overdose**

No experience with overdosage is available from human clinical trials. In clinical trials with Gazyvaro, doses ranging from 50 mg up to and including 2000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose-dependent.

Patients who experience overdose should have immediate interruption or reduction of their infusion and should be closely supervised. It should be borne in mind that patients require regular monitoring of blood count and for increased risk of infections while B cell-depleted.

# Properties/Effects

## ATC code

L01XC15

## Mechanism of action

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered type II anti-CD20 antibody of the IgG1 isotype. CD20 is expressed equally 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 tissues. Glycoengineering of the Fc part of obinutuzumab results in higher affinity for FcɣRIII receptors on immune effector cells such as natural killer (NK) cells, and macrophages and monocytes as compared to non-glycoengineered antibodies. In non-clinical studies, obinutuzumab induces direct cell death and mediates antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent phagocytosis (ADCP) through recruitment of FcɣRIII-positive effector cells. In addition, obinutuzumab mediates a low degree of complement-dependent cytotoxicity (CDC). In animal models, obinutuzumab mediates potent B cell depletion and antitumour efficacy.

## Pharmacodynamics

No information.

## Clinical efficacy

Chronic lymphocytic leukaemia

A phase III, open-label, three-arm study (BO21004/CLL11) in two parts compared Gazyvaro plus chlorambucil with MabThera plus chlorambucil or chlorambucil alone in 781 patients with previously untreated chronic lymphocytic leukaemia with comorbidities.

Patients had to have one or both of the following measures of coexisting medical conditions: comorbidity score (CIRS) of greater than 6 or reduced renal function (CrCl <70 ml/min). Patients with hepatic impairment and severe renal impairment were excluded from participating.

A total of 781 patients were randomised 2:2:1 to receive Gazyvaro plus chlorambucil, MabThera plus chlorambucil or chlorambucil alone. Stage 1 compared Gazyvaro plus chlorambucil to chlorambucil alone in 356 patients and stage 2 compared Gazyvaro plus chlorambucil to MabThera plus chlorambucil in 663 patients. The median age was 73 years.

The most frequently reported coexisting medical conditions were: 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%.

The primary endpoint of the study was investigator-assessed progression-free survival. This was 26.7 months for Gazyvaro plus chlorambucil vs 11.1 months for chlorambucil (HR 0.18 [95% CI 0.13, 0.24), p <0.0001) and 15.7 months for MabThera plus chlorambucil (HR 0.32 [95% CI 0.24, 0.44), p <0.0001). The difference Gazyvaro vs MabThera was also significant with HR 0.39 (95% CI 0.31, 0.49), p<0.0001. Analysis by an independent review committee produced similar results. The response rate was 78.4% in the Gazyvaro plus chlorambucil arm, 65% in the MabThera plus chlorambucil arm and 31.4% with chlorambucil alone.

26% of patients had molecular remission on treatment with Gazyvaro.

44% of patients treated with Gazyvaro plus chlorambucil were 75 years or older (median age was 73 years). These patients experienced more serious adverse events and adverse events leading to death than patients under 75 years of age. No significant differences in efficacy were observed between patients ≥75 years of age and those <75 years of age.

91% (40 out of 44) of evaluable patients treated with Gazyvaro displayed B cell depletion (defined as CD19+ B cell counts <0.07 × 109/l) at the end of the treatment period, which persisted during the 6-months of follow-up. Recovery of B cells was observed within 12 to 18 months of follow-up in 35% (14 out of 40) of patients without progressive disease and 13% (5 out of 40) with progressive disease.

At a later study cut-off date (10 October 2017), patients treated with Gazyvaro plus chlorambucil showed a clinically meaningful improvement in survival compared to both patients treated with chlorambucil alone and to patients treated with MabThera plus chlorambucil (OS HR 0.68 95% CI 0.49, 0.94 and HR 0.76 95% CI 0.60, 0.97). The mean observation period for OS data collection was 62.5 months for Gazyvaro plus chlorambucil vs chlorambucil (stage 1) and 59.4 months for Gazyvaro plus chlorambucil vs MabThera plus chlorambucil (stage 2).

## *Non-Hodgkin’s lymphoma (follicular lymphoma)*

Previously untreated follicular lymphoma

A multicentre, open-label, randomised phase III study (BO21223/GALLIUM) evaluated 1202 previously untreated patients with stage II (bulky disease)/III/IV follicular lymphoma (FL) grade 1‑3a. The patients had to require systemic treatment according to the GELF criteria. Patients were randomised 1:1 to receive either Gazyvaro or MabThera in combination with chemotherapy (CHOP, CVP or bendamustine), followed by Gazyvaro or MabThera maintenance therapy in patients with a complete or partial response. The demographic data and baseline characteristics in the FL population were well balanced between the treatment arms. Gazyvaro (1000 mg) was administered intravenously prior to chemotherapy (see “Dosage/Administration”). Bendamustine was administered at a dosage of 90 mg/m2/day intravenously in combination with Gazyvaro on days 1 and 2 in all treatment cycles (cycles 1‑6). CHOP and CVP were given at the standard dosage in combination with Gazyvaro. After cycles 6‑8, in which Gazyvaro was used in combination with chemotherapy, responding patients received Gazyvaro maintenance therapy every 2 months for 2 years or until disease progression. The primary efficacy analysis, based on investigator assessment after a median observation period of 35 months, showed a statistically significant 34% reduction in the risk of progressive disease (PD) or death in FL patients who received Gazyvaro + chemotherapy followed by Gazyvaro maintenance therapy compared to patients who received MabThera plus chemotherapy followed by MabThera maintenance therapy (hazard ratio [HR] 0.66; 95% CI: 0.51, 0.85, p-value [stratified log-rank test] = 0.0012).

##### Further important endpoints#

Supportive analysis of progression-free survival (PFS) as assessed by an independent review committee (IRC) showed a 29% reduction in the risk of PD or death (HR 0.71; 95% CI: 0.54, 0.93).

A total of 81 randomised patients had died: 46/601 patients (7.7%) in the MabThera plus chemotherapy arm and 35/601 patients (5.8%) in the Gazyvaro plus chemotherapy arm (HR 0.75 [95% CI: 0.49, 1.17]).

The estimated probability of being alive and not requiring new anti-lymphoma treatment (NALT) after 3 years was 81.2% (95% CI: 77.6, 84.2) in the MabThera plus chemotherapy arm and 87.1% (95% CI: 84.0, 89.6) in the Gazyvaro plus chemotherapy arm (HR 0.68 [95% CI: 0.51, 0.91]).

Based on investigator assessment (from CT scans according to 2007 IWG criteria), the overall response rate (complete [CR] or partial response) at the end of induction was 87% in the MabThera plus chemotherapy arm [95% CI: 83.9, 89.5] and 89% in the Gazyvaro plus chemotherapy arm (p = 0.33, Cochran-Mantel-Haenszel test). The CR rate was 24% in the MabThera plus chemotherapy arm (95% CI: 20.4, 27.4) and 20% in the Gazyvaro plus chemotherapy arm (95% CI: 16.4, 22.9). The investigator-assessed CR rates based on combined CT/positron emission tomography (PET) in a subgroup of 595 patients at the end of induction were 57% in the MabThera plus chemotherapy arm compared to 62% in the Gazyvaro plus chemotherapy arm.

*# not significant according to a sequential hierarchical testing procedure*

The results of the relevant PFS subgroup analyses were consistent overall with the results observed in the FL population.

## Relapsed/refractory follicular lymphoma

An open-label, multicentre, randomised phase III study (GAO4753g/GADOLIN) evaluated 396 patients with iNHL who had not responded to treatment with rituximab or a rituximab-containing regimen or in whom disease progression had occurred during or up to 6 months after such treatment. The patients were randomised 1:1 to treatment with bendamustine (B) alone (n = 202) or Gazyvaro in combination with bendamustine (G+B) (n = 194) for six 28-day cycles. Patients in the G+B arm who had not experienced disease progression by the end of induction treatment (i.e. patients with a complete response [CR], partial response [PR] or stable disease [SD]) continued to receive Gazyvaro as maintenance therapy until disease progression or for up to two years (whichever occurred first). Demographic and baseline data were well balanced (median age 63 years; the majority of patients were Caucasian [88%] and male [58%]). The median time from initial diagnosis was 3 years and the median number of prior therapies was 2 (range 1 to 10); 44% of patients had received one prior therapy, and 34% two prior therapies.

Obinutuzumab was administered as an intravenous 1000 mg dose on days 1, 8 and 15 of cycle 1, on day 1 of cycles 2‑6 and, in patients without disease progression, every 2 months for up to 2 years or until disease progression. Bendamustine was administered intravenously on days 1 and 2 of all treatment cycles (cycles 1‑6) at a dosage of 90 mg/m2/day when combined with Gazyvaro or 120 mg/m2/day when given alone.

The primary analysis, based on assessment by an independent review committee (IRC), showed a statistically significant and clinically meaningful 45% reduction in the risk of progressive disease (PD) or death in iNHL patients treated with G+B followed by G maintenance therapy compared to treatment with B alone (HR = 0.55, 95% CI: 0.39, 0.67; stratified log-rank test, p = 0.0001). At the time of the primary analysis, the median time to event in the B arm was 14.9 months (95% CI: 12.8, 16.6), while the median in the G+B arm had not been reached (95% CI: 22.5, not reached). The overall survival (OS) data were not yet mature. The IRC-assessed response rates at the end of induction treatment and the IRC-assessed best overall response within 12 months of treatment start were similar in both arms.

Most patients had follicular lymphoma (FL) (81.1%). The primary analysis in FL patients treated with G+B vs B alone showed a clinically meaningful IRC-assessed 52% reduction in the risk of PD or death (HR = 0.48, 95% CI: 0.34, 0.68). IRC-assessed median progression-free survival (PFS) in the B arm was 13.8 months, while the median in the G+B arm had not yet been reached.

Among the patients with non-follicular lymphoma, 11.6% had marginal zone lymphoma (MZL) and 7.1% small lymphocytic lymphoma (SLL). No conclusions can be drawn as to efficacy in MZL and SLL.

In the final analysis, the median observation period in FL patients was 45.9 months (range: 0-100.9) in the B arm and 57.3 months (range: 0.4-97.6) in the G+B arm, corresponding to an additional median observation period of 25.6 months and 35.2 months in the B and G+B arms, respectively, since the primary analysis. The final analysis reported only the investigator (INV)-assessed endpoints, as the assessments by the independent review committee (IRC) were not continued. Median PFS (INV-assessed) in the FL patient population was 24.1 months (95% CI: 17.4, 36.0) in the G+B arm vs 13.7 months (95% CI: 11.3, 15.3) in the B arm (HR = 0.51, 95% CI: 0.39, 0.67). There were 66 deaths (40.2%) in the G+B arm and 85 deaths (51.3%) in the B arm (OS HR = 0.71, 95% CI: 0.51, 0.98).

## Safety and efficacy in elderly patients

Non-Hodgkin’s lymphoma (mainly FL)

In the pivotal studies in iNHL, patients aged 65 years or older experienced more serious adverse events and adverse events leading to treatment discontinuation or death than patients under 65 years of age. No clinically meaningful differences in efficacy were observed.

#### Immunogenicity

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

No human anti-human antibodies (HAHAs) were observed after initiation of Gazyvaro in iNHL patients refractory to prior rituximab-containing therapy.

In previously untreated iNHL patients, 1/565 patients (0.2% of iNHL patients tested for HAHAs after initiation of Gazyvaro) developed HAHAs. The clinical significance of anti-obinutuzumab antibodies is not known. A potential correlation between anti-obinutuzumab antibodies and clinical course cannot be ruled out.

# Pharmacokinetics

All parameters shown in the sections below are estimates based on a population pharmacokinetic (PK) model.

## Absorption

After the cycle 6 day 1 infusion, the median Cmax value in CLL patients in the population model was 465.7 μg/ml and the median AUC(T) value was 8961 μg\*d/ml. In the iNHL patients, estimated median Cmax was 539.3 µg/ml and median AUC(T) 10,956 µg\*d/ml.

## Distribution

The volume of distribution at steady state is 2.72 l.

## Metabolism

The metabolism of Gazyvaro has not been directly studied. Antibodies are normally broken down in the liver like other proteins.

## Elimination

Gazyvaro clearance was approximately 0.11 l/day in CLL patients and 0.08 l/day in iNHL patients, with a median elimination half-life of 26.4 days in CLL patients and 36.8 days in iNHL patients.

## Kinetics in specific patient groups

There are no significant differences in exposure between women and men. Thus no dose adjustment is required for gender.

## *Hepatic impairment*

No formal pharmacokinetic studies have been conducted in patients with hepatic impairment.

## *Renal impairment*

No formal pharmacokinetic studies have been conducted in patients with renal impairment.

## *Elderly patients*

The population pharmacokinetic analysis of Gazyvaro showed no evidence that age affects the pharmacokinetics of Gazyvaro.

## *Children and adolescents*

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

# Preclinical data

## Carcinogenicity

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

## Genotoxicity

No studies have been performed to establish the genotoxic potential of Gazyvaro.

## Impairment of fertility

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

## Reproductive toxicity

An enhanced pre- and postnatal development (ePPND) toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received weekly intravenous Gazyvaro doses (mean AUC0‑168 h at steady state [on day 139 p.c.] was 125,000 and 250,000 [µg•h]/ml at 25 and 50 mg/kg, respectively; mean Cmax was 1220 and 2470 µg/ml at 25 and 50 mg/kg, respectively) during gestation (organogenesis period; post-conception day 20 until delivery). Exposed offspring did not exhibit any teratogenic effects but B cells were completely depleted on day 28 postpartum. Offspring exposures on day 28 postpartum suggest that Gazyvaro can cross the blood-placenta-barrier. Serum concentrations in the newborn on day 28 postpartum 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 the newborn must have occurred *in utero*. B cell counts returned to normal levels and immunological function was restored within 6 months of birth.

## Other

In a 26-week cynomolgus monkey study, hypersensitivity reactions were noted and attributed to recognition of the humanised antibody as foreign by cynomolgus monkeys (Cmax and AUC0‑168 h at steady state [day 176] after weekly administration of 5, 25 and 50 mg/kg were 377, 1530 and 2920 µg/ml and 39,800, 183,000 and 344,000 [µg•h]/ml, respectively). 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 euthanasia in 6/36 animals treated with Gazyvaro during dosing and recovery phases; these changes were partially reversible. Opportunistic infections were attributed to the pharmacological action of Gazyvaro.

# Other information

## Incompatibilities

After dilution with 0.9% sodium chloride, no incompatibilities were observed between Gazyvaro in the concentration range 0.4 mg/ml to 20.0 mg/ml and polyvinyl chloride/poly­ethylene/polypropylene/polyolefin infusion bags or polyvinyl chloride (PVC)/polyurethane (PUR)/polyethylene (PE) infusion sets, nor with optional inline filters with product contact surfaces of polyethersulfone (PES), a 3-way polycarbonate (PC) stopcock or polyetherurethane (PEU) catheters. Do not shake or freeze the diluted product.

Diluents other than 0.9% NaCl solution should not be used to dilute Gazyvaro since their use has not been studied.

## Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the container.

## Shelf life after opening

Gazyvaro does not contain antimicrobial preservatives. Therefore care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. Chemical and physical stability of the ready-to-use infusion solution has been demonstrated for 24 hours at 2‑8°C, followed by 24 hours at ambient temperature (≤30°C), followed by an infusion taking no longer than 24 hours.

For microbiological considerations, the prepared infusion solution should be used immediately. If the prepared solution cannot be administered immediately, the storage time and conditions prior to administration are the responsibility of the user and should not normally exceed 24 hours at 2-8°C, unless dilution has taken place under controlled and validated aseptic conditions.

## Special precautions for storage

Store in the refrigerator (2-8°C).

Do not shake. Do not freeze.

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

## Instructions for handling

Gazyvaro should be prepared by a healthcare professional under aseptic conditions. Use a sterile needle and syringe to prepare Gazyvaro.

## *CLL, first infusion (d1 and d2)*

To preclude mix-ups between the two infusion bags for the initial 1000 mg dose, the recommendation is to utilise bags of different sizes to distinguish between the 100 mg dose for cycle 1 day 1 and the 900 mg dose for cycle 1 day 1 (continued) or day 2. To prepare the two infusion bags, withdraw 40 ml of Gazyvaro concentrate from the vial and dilute 4 ml in a 100 ml infusion bag and the remaining 36 ml in a 250 ml PVC or PVC-free polyolefin infusion bag containing sterile, pyrogen-free 0.9% aqueous sodium chloride solution. Clearly label all infusion bags.

## *CLL, all subsequent infusions (cycle 1 d8 and d15 and cycles 2*‑*6) and FL, all infusions*

Withdraw 40 ml of Gazyvaro concentrate from the vial and dilute, for example, in PVC or PVC-free polyolefin infusion bags containing sterile, pyrogen-free 0.9% aqueous sodium chloride solution.

|  |  |  |
| --- | --- | --- |
| **Dose of Gazyvaro to be administered** | **Required amount of Gazyvaro concentrate** | **Size of PVC or PVC-free polyolefin infusion bag** |
| 100 mg | 4 ml | 100 ml |
| 900 mg | 36 ml | 250 ml |
| 1000 mg | 40 ml | 250 ml |

Diluents other than 0.9% NaCl solution should not be used (see “Incompatibilities”).

Gently invert the infusion bag to mix the solution and avoid excessive foaming.

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

## *Disposal of unused and expired medicinal product*

Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

# Packs

1000 mg vial: 1

**This is a medicament**

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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