# GAZYVARO® (obinutuzumab)

## CHECKLIST FOR THE TREATMENT OF PATIENTS WITH *FOLLICULAR LYMPHOMA (FL)* & *CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)*


CLL, chronic lymphocytic leukaemia; FL, follicular lymphoma.

Prescribing information can be found on pages 11-13.

# GAZYVARO INDICATIONS

## *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 FL*
- *Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of 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*

## *CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)*

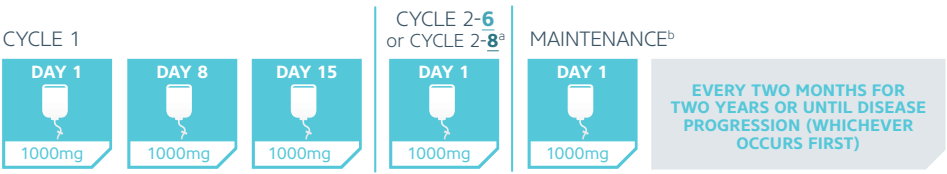
- *Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy*

CLL, chronic lymphocytic leukaemia; FL, follicular lymphoma.

# DOSING AND SCHEDULE

## *FOR FL PATIENTS*

**In FL all doses of Gazyvaro are 1000mg. There is no need for a split dose.**




### FIRST 1000mg ON DAY 1 CYCLE 1

**Administer at 50mg/hr. The rate of infusion can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.**

### ALL SUBSEQUENT INFUSIONS FROM DAY 8

**If no IRR occurred during the previous infusion, when the final infusion rate was 100mg/hr or faster, infusions can be started at a rate of 100mg/hr and increased by 100mg/hr increments every 30 minutes to a maximum of 400mg/hr.**

[a]Please note when:
- Gazyvaro is given with **bendamustine**, it is given for **six** 28 day cycles (in first-line and rituximab-refractory patients).
- Gazyvaro is given with **CHOP or CVP**, it is given for **eight** 21 day cycles (in first-line patients only).

[b]For patients who respond to induction treatment or have stable disease.

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; FL, follicular lymphoma; IRR, infusion-related reaction.

# INFUSION RATES

## *FOR FL PATIENTS*

| INFUSION RATES | | | | Gazyvaro infusion rates (mg/h) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 50 | 100 | 150 | 200 | 250 | 300 | 350 | 400 |
| **Gazyvaro treatment cycle** | **Gazyvaro dose (mg)** | **Gazyvaro volume (mL)** | **Final infusion volume (mL)** | **Gazyvaro infusion rates (mL/h)** | | | | | | | |
| Cycle 1, day 1 | 1000mg | 40mL | 250mL | **14** | 25 | 38 | 50 | 63 | 75 | 88 | 100 |
| Cycle 1, day 8, day 15 and cycles 2–6 | 1000mg | 40mL | 250mL | 14 | **25** | 38 | 50 | 63 | 75 | 88 | 100 |
| Maintenance | 1000mg | 40mL | 250mL | 14 | **25** | 38 | 50 | 63 | 75 | 88 | 100 |

Values in red represent recommended starting infusion rates for Gazyvaro.
**Note, these assume the patient has not experienced IRRs in the prior infusion**, otherwise the infusion rate should be no more than half the previous rate.

FL, follicular lymphoma; IRR, infusion-related reaction.

# DOSING AND SCHEDULE

## *FOR CLL PATIENTS*


**EACH CYCLE IS 28 DAYS IN DURATION**

CLL, chronic lymphocytic leukaemia.

# INFUSION RATES

## *FOR CLL PATIENTS*

| INFUSION RATES | | | | Gazyvaro infusion rates (mg/h) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 25 | 50 | 100 | 150 | 200 | 250 | 300 | 350 | 400 |
| **Gazyvaro treatment cycle** | **Gazyvaro dose (mg)** | **Gazyvaro volume (mL)** | **Final infusion volume (mL)[a]** | **Gazyvaro infusion rates (mL/h)** | | | | | | | | |
| Cycle 1, day 1 | 1000mg | 4mL | 100mL | **25** | N/A[b] | N/A[b] | N/A[b] | N/A[b] | N/A[b] | N/A[b] | N/A[b] | N/A[b] |
| Cycle 1, day 2 (or day 1 continued) | 900mg | 36mL | 250mL | 7 | **14** | 28 | 42 | 56 | 69 | 83 | 97 | 111 |
| Cycle 1, day 8, day 15 and cycles 2–6 | 1000mg | 40mL | 250mL | 6 | 13 | **25** | 38 | 50 | 63 | 75 | 88 | 100 |

Values in red represent recommended starting infusion rates for Gazyvaro.
**Note, these assume the patient has not experienced IRRs in the prior infusion**, otherwise the infusion rate should be no more than half the previous rate.

[a]Final infusion volume assumes that an equivalent volume of the diluent has been withdrawn to ensure the final volumes shown.
[b]Do not increase infusion rate in the first 100mg Gazyvaro infusion.
CLL, chronic lymphocytic leukaemia; IRR, infusion-related reaction.

# PREPARING YOUR FL AND CLL PATIENT FOR THEIR TREATMENT

- Reassure them about what they can expect when receiving their treatment
- Suggest they wear comfortable clothing to have their infusion
- Consider withholding hypertensive medicines for 12 hours before, during and 1 hour after infusions
- Prophylaxis with adequate hydration and administration of uricostatics (e.g. allopurinol), or a suitable alternative, starting 12–24 hours prior to the start of therapy is recommended for patients with high tumour burden and/or high circulating lymphocyte count (>25x$10^9$/L) and/or renal impairment (CrCl <70mL/min) to reduce the risk of Tumour Lysis Syndrome (TLS)
- Premedicate them before giving the infusion (see table on page 9)
- Consider a second cannula into the patient's other arm before infusion for the administration of symptomatic medication if any IRRs are experienced

CLL, chronic lymphocytic leukaemia; FL, follicular lymphoma; IRR, infusion-related reaction.

# PREPARING YOUR FL AND CLL PATIENT FOR THEIR TREATMENT (CONTINUED)

- Have emergency resuscitation facilities available during infusion
- Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period
- If a planned dose is missed, administer as soon as possible; do not wait until the next planned dose

## *IN ADDITION FOR CLL PATIENTS*

- Prepare them for the possibility of IRRs, particularly in advance of the first infusion on day 1 (and day 2 if infusion is split over 2 days)
- Monitor the patient closely during the first infusion, especially for the first 2 hours

CLL, chronic lymphocytic leukaemia; FL, follicular lymphoma; IRR, infusion-related reaction.

# PREMEDICATION

## *FOR FL AND CLL PATIENTS*

| | Cycle 1: Day 1 for FL Day 1 and 2 for CLL | Subsequent infusions | | |
|---|---|---|---|---|
| | **All patients** | **Patients without any IRR symptoms** | **Patients with grades 1–2 (mild to moderate) IRR** with the previous infusion | **Patients with a grade 3 (severe) IRR** with the previous infusion OR with a lymphocyte count >25x10$^9$/L prior to next treatment |
| Complete at least 60 minutes prior to infusion[a] **Intravenous corticosteroid** (100mg prednisone/prednisolone or 20mg dexamethasone or 80mg methylprednisolone)[b] | √√ | | | √√ |
| At least 30 minutes prior to infusion **Antihistaminic medicine** (e.g. 50mg diphenhydramine) | √√ | | √√ | √√ |
| At least 30 minutes prior to infusion **Oral analgesic/antipyretic** (e.g. 1000mg acetaminophen/paracetamol) | √√ | √√ | √√ | √√ |

[b]HYDROCORTISONE IS NOT RECOMMENDED AS IT HAS NOT BEEN EFFECTIVE IN REDUCING RATES OF INFUSION REACTIONS

[a]For CLL patients, if the 100mg infusion is completed without modifications of the infusion rate or interruptions, the 900mg infusion may be administered on the same day with no dose delay and no repetition of premedication necessary.
CLL, chronic lymphocytic leukaemia; FL, follicular lymphoma; IRR, infusion-related reaction.

# INFUSION-RELATED REACTION (IRR) MANAGEMENT

## *FOR FL AND CLL PATIENTS*

| IRR grade | Recommendation |
|---|---|
| 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<br>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)<br>If the patient does not experience any further IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose<br>If the patient experiences a second occurrence of a grade 3 IRR, the infusion must be stopped and therapy permanently discontinued<br>For CLL patients, the day 1 (cycle 1) infusion rate may be increased back up to 25mg/h after 1 hour, but not increased further |
| Grade 1–2 (mild to moderate) | The infusion rate must be reduced and symptoms treated<br>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)<br>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<br>For CLL patients, the day 1 (cycle 1) infusion rate may be increased back up to 25mg/h after 1 hour, but not increased further |

CLL, chronic lymphocytic leukaemia; FL, follicular lymphoma; IRR, infusion-related reaction.

# PRESCRIBING INFORMATION

**Gazyvaro® (obinutuzumab) 1000 mg concentrate for solution for infusion** Please refer to Gazyvaro SmPC for full prescribing information. **Indications:** Chronic Lymphocytic Leukaemia (CLL): Use with chlorambucil for those with previously untreated CLL unsuitable for full-dose fludarabine therapy. Follicular Lymphoma (FL): Use with chemotherapy and then as maintenance, for those with previously untreated advanced FL. Use with bendamustine and then as maintenance, for FL patients who did not respond or who progressed during or up to 6 months after treatment with a rituximab-containing regimen. **Dosage and administration:** Administer as an IV infusion through a dedicated line, with full resuscitation facilities immediately available. Administer premedication before each infusion, consider withholding antihypertensive medications prior to and throughout infusion, see SmPC for further details. Consider prophylaxis for Tumour Lysis Syndrome (TLS), see SmPC for further details. If appropriate, repeat prophylaxis prior to each infusion. *CLL: Dose*: Cycle 1: 1000 mg split over Day 1, 100 mg (25 mg/hr) and Day 2, 900 mg (or Day 1 continued, if no (infusion related reaction) IRR occurred, at 50 mg/hr), 1000 mg on Days 8 and 15. Cycles 2–6: 1000 mg on Day 1; six 28-day treatment cycles. Infusion rate can be escalated in 50 mg/hr increments every 30 minutes to 400 mg/hr. If an IRR occurred previously, start at 25 mg/hr and increase in increments of 50 mg/hr every 30 minutes to 400 mg/hr. *All subsequent infusions*: if no IRR occurred previously, when final rate was 100 mg/hr or faster, start at 100 mg/hr and increase by 100 mg/hr increments every 30 minutes to 400 mg/hr. If an IRR occurred during previous infusion, start at 50 mg/hr and increase in increments of 50 mg/hr every 30 minutes up to 400 mg/hr. *FL*: *Dose (previously untreated patients)*: Induction; six 28-day cycles with bendamustine; six 21-day cycles in combination with CHOP, followed by 2 additional cycles of Gazyvaro alone; or eight 21-day cycles in combination with CVP. Cycle 1: 1000 mg on Days 1, 8 and 15. Cycles 2 onwards: 1000 mg on Day 1. Patients who achieve a response to induction treatment should receive Gazyvaro maintenance for up to two years, 1000 mg once every 2 months or until disease progression. *Relapse/Refractory:* Induction in combination with bendamustine and maintenance schedules (Cycles 2-6) are as above for FL. *Administration*: *Cycle 1*: *Day 1 (1000 mg)*: administer at 50 mg/hr, may be escalated in 50 mg/hr increments every 30 minutes to 400 mg/hr. *All subsequent infusions*: if no IRR or a Grade 1 IRR occurred during previous infusion when final rate was 100 mg/hr or faster, start at 100 mg/hr and increase by 100 mg/hr every 30 minutes to 400 mg/hr. If an IRR of Grade 2 or higher previously occurred start at 50 mg/hr; increase by 50 mg/hr every 30 minutes to 400 mg/hr. Management of IRRs may require temporary interruption, reduction in infusion rate or discontinuation, see SmPC

# PRESCRIBING INFORMATION (CONTINUED)

for further details. **Contra-indications:** Hypersensitivity to any component of this product. **Precautions:** *IRRs:* predominantly during infusion of first 1000 mg. Do not administer further infusions if a patient experiences acute life threatening respiratory symptoms or a Grade 4 or second Grade 3 reaction. Cytokine release syndrome has been reported. CLL patients with a high tumour burden and/or circulating lymphocyte count of >25 $x10^9$/L may be at increased risk of severe IRRs. Exercise caution in patients with renal impairment (CrCl <50 mL/min) and with both Cumulative Illness Rating Scale (CIRS) >6 and CrCl <70 mL/min. Carefully monitor patients who have pre-existing cardiac or pulmonary conditions throughout the infusion and post-infusion period. *Hypersensitivity reactions including anaphylaxis*: if suspected, stop the infusion and permanently discontinue Gazyvaro. *TLS* has been reported, see SmPC for further details. Renal function, potassium, and uric acid values in patients at risk should be monitored during initial treatment period. *Neutropenia*: Neutropenia including febrile neutropenia has been reported more frequently in patients with renal impairment (CrCl <50 mL/min). Neutropenic patients should be closely monitored until resolution. Consider dose delays with severe or life threatening neutropenia. Late onset neutropenia (occurring >28 days later) and prolonged neutropenia (lasting >28 days after treatment end) may occur. *Thrombocytopenia*: acute (within 24 hours after infusion), severe and life-threatening has been observed more frequently with renal impairment (CrCl <50 mL/min). Fatal haemorrhagic events have also been reported in Cycle 1. Monitor patients closely during the first cycle; perform regular laboratory tests until event resolution, consider dose delays. *Worsening of pre-existing cardiac conditions*: may occur as part of an IRR and can be fatal. Patients with cardiac disease should be monitored closely and hydrated with caution to prevent fluid overload. *Infections*: do not administer in the presence of an active infection and exercise caution in patients with a history of recurring or chronic infections. CLL patients with a CIRS >6 and CrCl <70 mL/min are more at risk. In FL patients, high incidence of infections was observed with Grade 3-5 more frequently in those who received Gazyvaro plus bendamustine in the induction phase. *Hepatitis B virus (HBV) reactivation*: and subsequent complications can occur in patients treated with anti-CD20 antibodies. Perform HBV screening (HBsAg and HBcAb-status) before initiating treatment. Patients with active HBV should not be treated and those with positive hepatitis B serology should consult a hepatologist before starting treatment. *Progressive Multifocal Leukoencephalopathy (PML)*: consider in any patient with new-onset or changes to pre-existing neurologic conditions. Withhold treatment during investigation of potential PML, permanently discontinued if confirmed and

# PRESCRIBING INFORMATION (CONTINUED)

refer patient to a neurologist. *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. *Fertility, pregnancy and lactation:* Women of childbearing potential must use effective contraception during and for 18 months after treatment. Women should discontinue breast-feeding during Gazyvaro therapy and for 18 months after the last dose. **Adverse reactions**: see SmPC for further details. *Very common/common*: IRRs, urinary tract infection, upper respiratory tract infection, pneumonia, herpes zoster, oral herpes, influenza, squamous cell carcinoma of skin, basal cell carcinoma, febrile neutropenia, leukopenia, thrombocytopenia, anaemia, TLS, hyperuricaemia, hypokalaemia, insomnia, depression, anxiety, fatigue, atrial fibrillation, hypertension, cough, nasal congestion, rhinorrhoea, constipation, diarrhoea, dyspepsia, haemorrhoids, alopecia, pruritus, eczema, dysuria, urinary incontinence, asthenia, weight increase, headache, oropharyngeal pain, arthralgia, back pain, chest pain, pain in extremity and pyrexia. *Serious reactions*: IRRs, TLS, thrombocytopenia, PML, bacterial, fungal and new or re-activated viral infections, gastro-intestinal perforation, severe haemorrhagic events, worsening of pre-existing cardiac conditions. *Special populations*: patients with renal impairment (CrCl <50 mL/min) and older patients (CLL: ≥75 years / FL: ≥65 years) experienced more SAEs and AEs leading to treatment withdrawal or death. **Legal Category:** POM **NHS Costs:** 1000 mg of obinutuzumab in 40 mL (25 mg/mL) pack of 1 vial: £3,312 **Marketing Authorisation Number:** EU/1/14/937/001 **Supplied by**: Roche Products Limited, 6 Falcon Way, Welwyn Garden City, Herts, AL71TW**.** GAZYVARO is a registered trade mark. M-GB-00000161 **Date of Preparation:** June 2020

Adverse events should be reported.

Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554.

As Gazyvaro is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.

**Reference:** 1. Gazyvaro Summary of Product Characteristics.

# RESOURCES

For full details about Gazyvaro, please see the Summary of Product Characteristics here:
**http://bit.ly/2E2pl6A**

## *ROCHE RESOURCES*

For additional information about Gazyvaro including the mode of action, efficacy and safety data and FAQs please visit Roche Resources.

Please find safety information for Gazyvaro on Roche Resources here:
**https://bit.ly/2DT2sna**

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