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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 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.

Table 1 Premedication to be administered before Gazyvaro infusion to reduce the risk of IRRs in 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 Patients with lymphocyte counts $>25 \times 10^9/L$ 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

- ¹ 100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
- ² e.g. 1000 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 medicinal product 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 1000 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 1000 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	1000 mg
	Day 15	1000 mg
Cycles 2-6	Day 1	1000 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 1000 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 1000 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	1000 mg
	Day 8	1000 mg
	Day 15	1000 mg
Cycles 2–6 or 2-8	Day 1	1000 mg
Maintenance	Every 2 months for 2 years or until disease progression (whichever occurs first)	1000 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 - 6.

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
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 (1000 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.
Cycles 2-6	Day 15 (1000 mg)	
	Day 1 (1000 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.

Follicular lymphoma (FL)

Gazyvaro should be administered at the standard infusion rate in Cycle 1 (see Table 5). In patients who do not experience Grade ≥ 3 infusion related reactions (IRRs) during Cycle 1, Gazyvaro may be administered as a short (approximately 90 minute) duration infusion (SDI) from Cycle 2 onwards (see Table 6).

Table 5 Follicular lymphoma: Standard infusion rate and recommendations in case an IRR occurred with previous infusion

Cycle	Day of treatment	Rate of infusion
Cycle 1	Day 1 (1000 mg)	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". 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 (1000 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 (1000 mg)	
Cycles 2–6 or 2–8	Day 1 (1000 mg)	
Maintenance	Every 2 months for 2 years or until disease progression (whichever occurs first)	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.

Table 6 Follicular lymphoma: Short duration infusion rate and recommendations in case an IRR occurred with previous infusion

Cycle	Day of treatment	Rate of infusion
Cycles 2–6 or 2–8	Day 1 (1000 mg)	For management of IRRs that occur during the infusion, refer to "Management of IRRs". If no IRR of Grade ≥ 3 occurred during Cycle 1: 100 mg/hr for 30 minutes, then 900 mg/hr for approximately 60 minutes. If an IRR of Grade 1-2 with ongoing symptoms or a Grade 3 IRR occurred during the previous SDI infusion, administer the next obinutuzumab infusion at the standard rate (see Table 5).
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 - 6). For CLL patients receiving the Day 1 (Cycle 1) dose split over two days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.
- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 4 - 6). For CLL patients receiving the Day 1 (Cycle 1) dose split over two days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

Management of IRRs occurring during SDI

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and not greater than 400 mg/hr. If the patient experiences a second Grade 3 IRR after resuming the infusion, the infusion must be stopped and therapy must be permanently discontinued. If the patient is able to complete the infusion without further Grade 3 IRRs, the next infusion should be given at a rate not higher than the standard rate.
- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Tables 5-6).

Instructions for dilution

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

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 1000 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
1000 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 $\leq 30^\circ\text{C}$.

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.

Disposal

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