Infusing GAZYVA®
(obinutuzumab)
& management of infusion-related reactions

**Indication**

GAZYVA in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) and rituximab-refractory follicular lymphoma (R/R FL).¹
GAZYVA is administered intravenously in 6 treatment cycles, each 28 days in duration.1

For Days 1 and 2 of Cycle 1, the 1000 mg GAZYVA vial will be split between 100 mg and 900 mg, respectively.1

For Cycles 1 to 6, chlorambucil (Clb) is administered orally on Days 1 and 15 at 0.5 mg/kg.1

Administration

- Administer as an intravenous infusion through a dedicated line, in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced physician. Do not administer as an intravenous push or bolus.1

- No incompatibilities between GAZYVA and polyvinyl chloride (PVC) or non-PVC polyolefin bags and administration sets have been observed in concentration ranges from 0.4 mg/mL to 20 mg/mL after dilution of GAZYVA with 0.9% sodium chloride.1
First GAZYVA infusion¹

**CYCLE 1 (FIRST 1000 mg)**

- **BAG 1**
  - **DAY 1**: 100 mg
  - Any infusion-related symptoms?
    - Yes ➔ **DAY 2**: 900 mg
    - No ➔ **DAY 1**: 900 mg

GAZYVA infusion rate¹

**BAG 1 (first 100 mg)** Start at 25 mg/h over 4 hours. Do not increase the infusion rate.

**BAG 2 (remaining 900 mg)** Start at 50 mg/h. Rate can be increased by 50 mg/h every 30 minutes to a maximum rate of 400 mg/h.

**DAY 1**: If patients can tolerate the first 100 mg infusion at a rate of 25 mg/h over 4 hours, it is possible to continue to infuse the remaining 900 mg of the dose within 1 day. A total time of at least 8 hours will be required.

Subsequent 1000 mg doses¹

- Each cycle is 28 days duration

**CYCLE 1 (CONTINUED)**

- **DAY 8**: 1000 mg
- **DAY 15**: 1000 mg
- **DAY 28**:

**CYCLES 2–6**

- **DAY 1**: 1000 mg
- **DAY 8**: 1000 mg
- **DAY 15**: 1000 mg
- **DAY 28**:

**CYCLE 1: DAYS 8, 15 AND CYCLES 2–6: DAY 1**

Start at 100 mg/h. Rate can be increased by 100 mg/h every 30 minutes, to a maximum of 400 mg/h.
PREMEDICATION\(^1\)

Premedication is highly recommended to reduce the risk of infusion-related reactions (IRRs)\(^1\)

<table>
<thead>
<tr>
<th>CYCLE 1: DAYS 1 AND 2</th>
<th>SUBSEQUENT INFUSIONS</th>
</tr>
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<tbody>
<tr>
<td>All patients</td>
<td>Patients without any IRR symptoms</td>
</tr>
</tbody>
</table>

- **COMPLETE 60 MINUTES PRIOR TO INFUSION**
  - Intravenous corticosteroid (20 mg dexamethasone or 80 mg methylprednisolone)\(^2\)

- **30 MINUTES PRIOR TO INFUSION**
  - Antihistamine medicine (e.g. H1 histamine receptor blockade)

- **30 MINUTES PRIOR TO INFUSION**
  - Oral analgesic/antipyretic (e.g. 1000 mg paracetamol)

\(^2\)Hydrocortisone is not recommended, as it has not been effective in reducing rates of IRRs.
Preparing patients for infusion

- Ensure patients drink plenty of water to remain hydrated, even if they don’t feel thirsty
- As for any medical intervention, patients should consider having someone drive them home
- If the decision has been made to withdraw antihypertensive treatment, remind patients to not take their antihypertensive medication for 12 hours prior to and throughout each GAZYVA infusion, and for the first hour after administration

Prior to administration - TLS prophylaxis

Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 10⁹/L) and/or renal impairment (CrCl < 70 mL/min) are considered at risk of tumour lysis syndrome (TLS) and should receive prophylaxis prior to GAZYVA administration

- 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)
- 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
- Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate
Prior to administration - Withholding antihypertensives

- Hypotension may occur during GAZYVA intravenous infusions. Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each GAZYVA infusion, and for the first hour after administration.

For detailed GAZYVA safety information and precautions, please refer to the GAZYVA Data Sheet.
PREPARATION

Prepare the solution for infusion, using aseptic technique, as follows:

1. Inspect visually for any particulate matter and discolouration prior to administration

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

3. Withdraw the appropriate volume of GAZYVA solution from the vial

<table>
<thead>
<tr>
<th>VOLUME OF GAZYVA TO ADMINISTER FOR VARIOUS DOSES</th>
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<tbody>
<tr>
<td>Dose of GAZYVA to be administered</td>
</tr>
<tr>
<td>100 mg</td>
</tr>
<tr>
<td>900 mg</td>
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<tr>
<td>1000 mg</td>
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4. Dilute into a 250 mL 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag. Other diluents such as dextrose (5%) solution should not be used

   Note: For treatment cycle 1, utilise bags of different sizes to distinguish between the 100 mg dose and the 900 mg dose. To prepare the two infusion bags, withdraw 40 mL GAZYVA from vial, and dilute 4 mL into a 100 mL infusion bag and the remaining 36 mL into a 250 mL infusion bag. Clearly label each infusion bag

5. Mix diluted solution by gentle inversion. Do not shake or freeze

6. Physical and chemical stability of the prepared infusion solution of GAZYVA has been demonstrated for 24 hours at 2°C–8°C followed by 24 hours at ambient temperature (≤30°C) followed by an infusion taking no longer than 24 hours. To reduce microbiological hazard, the prepared infusion solution should be used immediately. If storage is necessary, hold at 2°C–8°C for not more than 24 hours

For information on how to store GAZYVA properly, please refer to the GAZYVA Data Sheet.

Dosage forms and strengths

- 1000 mg/40 mL (25 mg/mL) single-use vial
INFUSION-RELATED REACTIONS (IRRs) DEFINITION & GRADING

- IRRs are adverse events that occur during or within 24 hours of receiving an IV monoclonal antibody (mAb) infusion
- Clinical signs vary in severity and can include many different symptoms involving different body systems
- 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 to be at risk of tumour lysis syndrome

Symptoms most commonly associated with an IRR in patients treated with GAZYVA

<table>
<thead>
<tr>
<th>IRR SYMPTOMS</th>
<th>G-Clb PATIENTS n (%) (n=336)</th>
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</thead>
<tbody>
<tr>
<td>General/administration-site disorders</td>
<td>119 (35)</td>
</tr>
<tr>
<td>Chills</td>
<td>78 (23)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>70 (21)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>109 (32)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>65 (19)</td>
</tr>
<tr>
<td>Flushing</td>
<td>41 (12)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>94 (28)</td>
</tr>
<tr>
<td>Nausea</td>
<td>73 (22)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>54 (16)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td>65 (19)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>47 (14)</td>
</tr>
<tr>
<td><strong>Nervous system disorders (e.g. headaches, dizziness)</strong></td>
<td>33 (10)</td>
</tr>
</tbody>
</table>

IRR = infusion-related reaction; G-Clb = GAZYVA plus chlorambucil. Data adapted from Roche Data on File.
**IRR*rs vs hypersensitivity (allergic) reactions**

IRR*rs are different to hypersensitivity reactions:*2

- Hypersensitivity reactions to GAZYVA typically occur after previous exposure and very rarely with the first infusion. Hypersensitivity reactions tend to increase with repeated administration of the allergen.

Hypersensitivity reactions may be difficult to distinguish from IRR*rs, however there are some important differences between the two:*2

<table>
<thead>
<tr>
<th></th>
<th>IRR*rs</th>
<th>HYPERSENSITIVITY (ALLERGIC) REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aetiology</strong></td>
<td>Mediated by cytokines, released as a result of the monoclonal antibody*2</td>
<td>Mediated by IgE*2</td>
</tr>
<tr>
<td><strong>Frequency/Timing</strong></td>
<td>Commonly occur with monoclonal antibody therapy. Most occur during, or within 24 hours of, the first infusion*1,*2</td>
<td>Typically occur only after multiple infusions. Usually within minutes of exposure, although delayed reactions (10-12 hours later) can arise*2</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Tend to subside with each subsequent infusion*2</td>
<td>Tend to occur more frequently and with increasing severity with subsequent infusions*2</td>
</tr>
</tbody>
</table>

*IRR* = infusion-related reaction; IgE = Immunoglobulin E.
Management of reactions during a GAZYVA infusion

• If a **hypersensitivity reaction** is suspected, the infusion should be stopped and GAZYVA treatment permanently discontinued. Manage with supportive care.

• If an **IRR** is suspected (Grade 1–3), the infusion should be slowed or interrupted. Manage with premedication and supportive care. **GAZYVA should be permanently stopped if a patient experiences a Grade 4 IRR or a second Grade 3 IRR**.

**Terminology for the classification of IRRs**

The National Cancer Institute classifications for IRRs according to the Common Terminology Criteria for Adverse Events (CTCAE) are:

<table>
<thead>
<tr>
<th>CTCAE GRADE</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>1</td>
<td><strong>Mild</strong> transient reaction; infusion interruption not indicated; intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td><strong>Therapy or infusion interruption indicated</strong>, but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours</td>
</tr>
<tr>
<td>3</td>
<td><strong>Prolonged</strong> (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae</td>
</tr>
<tr>
<td>4</td>
<td><strong>Life-threatening</strong> consequences: urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td><strong>Death</strong></td>
</tr>
</tbody>
</table>

**IRR** = infusion-related reaction; **IV** = intravenous; **NSAID** = non-steroidal anti-inflammatory drug.
CLL11 STUDY: IRRs WERE INFREQUENT AFTER THE FIRST DOSE OF GAZYVA $^{1,6,7}$

- IRRs were the most frequent adverse event in the CLL11 study, occurring in 66% (n=221) of patients treated with GAZYVA + chlorambucil (G-Clb) vs 38% (n=121) of patients treated with MabThera® (rituximab) + chlorambucil (R-Clb)$^6,7$

- Increased IRRs with GAZYVA were noted especially during the first 1000 mg administered (Day 1 and Day 2) when all of the grade 3/4 IRRs occurred$^1,7$

- At all subsequent infusions, only grade 1 and 2 IRRs were reported with GAZYVA. These occurred at a low rate, with only 3% of patients experiencing IRRs with the second GAZYVA dose and ≤1% at later doses$^1,7$

- In the majority of patients, 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$^1$

- 7% (n=25) of patients treated with GAZYVA + chlorambucil discontinued the trial due to IRRs. No fatal IRRs occurred$^1,7$

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The most common symptoms of IRRs for G-Clb are chills, nausea, pyrexia, hypotension and vomiting.$^{1,3}$

IRR = infusion-related reaction; G-Clb = GAZYVA plus chlorambucil.
Appropriate management of IRRs is important so patients are able to receive the recommended six cycles of treatment.\textsuperscript{1,6}
No grade 5 IRRs occurred. Patients with grade 4 or recurring grade 3 IRRs were discontinued (per protocol); 7% of patients in the G-Clb arm discontinued due to IRRs; 81% of patients received the 6 cycles of GAZYVA.1,7

G-Clb = GAZYVA plus chlorambucil; R-Clb = rituximab plus chlorambucil; IRR = infusion-related reaction.
HOW TO ADJUST THE INFUSION IF AN IRR OCCURS

<table>
<thead>
<tr>
<th>Grade 4 (life threatening)</th>
<th>• Stop infusion and permanently discontinue therapy</th>
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</table>
| Grade 3 (severe)          | • Temporarily interrupt infusion and treat symptoms as appropriate  
|                           | • Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) 
|                           | • If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose\(^\ast\). The Day 1 infusion rate may be increased back to 25 mg/h after 60 minutes, but not increased further  
|                           | • Stop infusion and permanently discontinue therapy if patients experience a second occurrence of a Grade 3 IRR |
| Grade 1–2 (mild to moderate) | • Reduce infusion rate and treat symptoms as appropriate  
|                           | • Upon resolution of symptoms, continue infusion  
|                           | • If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose\(^\ast\). The Day 1 infusion rate may be increased back to 25 mg/h after 60 minutes, but not increased further |

\(^\ast\)If GAZYVA is not tolerated, use a rate of 25 mg/h; IRR = infusion-related reaction.

Patients should not receive further GAZYVA infusions if they experience:\(^1\)

- Acute life-threatening respiratory or anaphylactoid symptoms
- A Grade 4 (life-threatening) IRR
- A second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion)
Dosing modification^1

- No dose modification of GAZYVA is recommended
- Infusion should be interrupted or slowed if patients experience Grade 1-3 IRRs
- If the previous infusion rate was not well tolerated, instructions for the Cycle 1, Day 1 and Day 2 infusion rate should be used
- If a planned dose of GAZYVA is missed, it should be administered as soon as possible and the next cycle should begin 28 days later; do not wait until the next planned dose

IRR = infusion-related reaction.
GAZYVA® (obinutuzumab) ABRIDGED PRESCRIBING INFORMATION.

GAZYVA concentrate solution for IV infusion (1000mg/40mL; 25 mg/mL, packs of 1) is a Prescription Medicine indicated for: in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL); in combination with bendamustine followed by GAZYVA maintenance for the treatment of patients with indolent non-Hodgkin lymphoma (iNHL) who did not respond to, or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. Dosage & Administration: Please refer to the GAZYVA Data Sheet for information. Contraindications: Patients with a known hypersensitivity (IgE mediated) to obinutuzumab or to any of the excipients. Precautions: Severe, life-threatening infusion related reactions (IRRs) have been reported. Follow premedication instructions and modify infusion rate as advised under Dosage & Administration (see Data Sheet). Stop infusion and permanently discontinue for Grade 4 IRRs, second occurrence of Grade 3 IRR or acute life-threatening respiratory symptoms. Carefully monitor patients with pre-existing cardiac or pulmonary conditions. Consider withholding antihypertensive medication for 12 hours prior to, during, and the first hour after infusion. Hypersensitivity including anaphylaxis; stop and discontinue permanently in these patients. Patients at high risk of tumour lysis syndrome (TLS) should receive prophylaxis with uricosuric and hydration starting 12-24 hrs prior to infusion. For TLS treatment, correct electrolyte abnormalities, monitor renal function and fluid balance; administer supportive care, including dialysis as indicated. All at risk patients should be carefully monitored during initial treatment. Severe/life-threatening neutropenia including febrile neutropenia, late onset, and prolonged neutropenia have been reported. Closely monitor patients until resolution. Treat concomitant infection; consider G-CSF therapy. Severe/life-threatening thrombocytopenia including acute thrombocytopenia, and fatal haemorrhagic events have been reported during Cycle 1 infusion. Closely monitor patients; perform regular laboratory tests until the event resolves. Transfusion of blood products is at the discretion of the treating physician. Worsening of pre-existing cardiac conditions has been observed in patients with underlying cardiac disease. These events may occur as part of an IRR and can be fatal. Closely monitor patients with a history of cardiac disease. Hydrate with caution. Do not administer to patients with active infections and exercise caution in those 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 therapy. Potential HBV reactivation; screen all patients prior to treatment. Do not treat patients with active disease and refer patients with positive serology to a specialist before commencing treatment. Progressive multifocal leucoencephalopathy (PML) has been reported in patients treated with GAZYVA. Consider PML in any patient presenting with new-onset neurologic manifestations. Withhold treatment during investigation and permanently discontinue if PML is confirmed. Immunisation with live virus vaccines is not recommended until B-cell recovery. In the pivotal trial patients with moderate renal impairment (CrCl <50 mL/min) experienced more SAEs and AEs leading to death than those with CrCl ≥50 mL/min. Safety and efficacy in patients with hepatic impairment and in paediatric patients (<18 years old) have not been established. Elderly patients (≥75 years old) experienced more SAEs and AEs leading to death than those <75 years old in the pivotal trial. Patients experiencing infusion-related symptoms should not drive or operate machines until symptoms abate. No formal drug-drug interaction studies have been performed. Pregnancy: Category C. Avoid treatment during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. Use effective contraception during treatment and for 18 months following treatment. Discontinue breast-feeding during therapy and for 18 months after the last dose. Newborns to mothers who have been exposed to GAZYVA during pregnancy should not receive live vaccines until B-cell levels are within normal ranges. Adverse Effects: (See Data Sheet for complete list). IRRs characterised by nausea, fatigue, chills, hypotension, pyrexia, vomiting, dyspnea, flushing, hypertension, headache, tachycardia, dizziness and diarrhoea; respiratory and cardiac symptoms including bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and atrial fibrillation. Neutropenia, thrombocytopenia, leucopenia, anaemia, lymph node pain, cardiac failure, ocular hyperaemia, dyspepsia, colitis, haemorrhoids, constipation, asthenia, chest pain, upper respiratory tract infection, sinusitis, lung infection, influenza, urinary tract infection, oral herpes, rhinitis, pharyngitis, nasopharyngitis, cough, nasal congestion, rhinorrhea, TLS, hyperuricaemia, arthralgia, back, bone, extremity and musculoskeletal chest pain, depression, dysuria, urinary incontinence, decreased WBC count, decreased neutrophil count, weight increase, squamous cell carcinoma of skin, alopecia, pruritus, night sweats, eczema. Transient elevation in liver enzymes shortly after the first infusion. Cases of gastro-intestinal perforation have been reported, mainly in NHL patients. GAZYVA is a funded medicine for patients with chronic lymphocytic leukaemia or indolent non Hodgkin lymphoma. Before prescribing, please review the GAZYVA Data Sheet available at www.medsafe.govt.nz. API based on Data Sheet 15.06.2016. Roche Products (New Zealand) Limited, Auckland. Ph 0800 656 464. www.roche.co.nz All trademarks mentioned herein are protected by law. References: 1. GAZYVA Data Sheet 16/10/2016. 2. Vogel WH. Clin J Oncol Nurs 2010; 14:E10–E21. 3. Snowden A, et al. Int J Nurs Pract 2015; 21(suppl 3):15–27. 4. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010). Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_Sx7.pdf. Accessed Nov 2016. 5. Roche Data on File (GA2004). 6. Goede V, et al. N Engl J Med 2014; 370:1101–1110. 7. Goede V, et al. N Engl J Med 2014; 370:1110–1110. DOI: 10.1056/NEJMoa1313984. Supplementary Appendix. ID2428/NA8775/Dec 2016.