Prescribing information: Gazyvaro® ▼ (obinutuzumab)

PRESCRIBING INFORMATION

Gazyvaro® (obinutuzumab) 1000 mg concentrate for solution for infusion

Refer to Gazyvaro Summary of Product Characteristics (SmPC) for full prescribing information.

Indications: Previously-untreated chronic lymphocytic leukaemia (CLL), in combination with chlorambucil, in patients with co-morbidities making them unsuitable for full-dose fludarabine-based therapy. Follicular lymphoma (FL), in combination with bendamustine followed by Gazyvaro maintenance, in patients who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Dosage and Administration: Administer as an IV infusion through a dedicated line, with full resuscitation facilities immediately available and under supervision of an experienced physician. Do not administer as IV push or bolus. Administer premedication before each infusion - see SmPC for further details. Consider withholding antihypertensives for 12 hours prior to and throughout each infusion and for the first hour after administration. Prophylaxis for Tumour Lysis Syndrome (TLS): adequate hydration and uricostatics (started at least 12–24 hours prior to start of Gazyvaro infusion as per standard practice) recommended in patients with a high tumour burden and/or where lymphocyte count >25 x 10^9/L and/or with renal impairment (CrCl<70mL/min). If appropriate, repeat prophylaxis prior to each infusion. Dose: CLL: Cycle 1: 1000 mg split over Day 1 (100 mg) and Day 2 (or Day 1 continued) (900 mg), 1000 mg on Day 8 and 15. Cycles 2 - 6: 1000 mg on day 1; and each cycle 28 days duration. **FL:** Cycle 1: 1000 mg on Day 1, 8 and 15. Cycles 2 - 6: 1000 mg on day 1. Each cycle 28 days duration. FL patients responding to induction treatment or who have stable disease should receive Gazyvaro maintenance as a single agent, 1000 mg once every 2 months for 2 years or until disease progression (whichever occurs first). *Administration:* Monitor closely for infusion related reactions (IRRs). **CLL:** *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 prior infusion administer at 50 mg/hr. Infusion rate can be escalated in 50 mg/hr increments every 30 minutes to 400 mg/hr. – All subsequent infusions: If no IRR occurred during prior infusion 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. **FL:** *Cycle 1: Day 1 (1000 mg):* Administer at 50 mg/hr, and increase over 30 minute increments to a maximum of 400 mg/hr. All subsequent infusions: If no IRR occurred during prior infusion 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. Management of IRRs may require temporary interruption, reduction in rate of infusion, or treatment discontinuations – see SmPC for further details.

Contra-indications: Hypersensitivity to any component of this product.

Precautions: Record the trade name and batch number in the patient record to improve traceability of biological medicinal products.

IRRs: Most frequently observed during infusion of first 1000 mg with most patients having no IRRs during subsequent administrations. Mitigation measures to reduce IRRs should be followed, see SmPC. IRRs may be related to cytokine release syndrome which has been reported in patients treated with Gazyvaro. Patients with a high tumour burden and/or high circulating lymphocyte count in CLL (> 25 x 10^9/L) may be at increased risk of severe IRRs. Patients with renal impairment (CrCl < 50 mL/min) and with both Cumulative Illness Rating Scale (CIRS) > 6 and CrCl < 70 mL/min are more at risk of IRRs, including severe IRRs. Do not administer further infusions if patient experiences acute life-threatening respiratory symptoms, a Grade 4 (life threatening) IRR or, a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion). Carefully monitor patients who have pre-existing cardiac or pulmonary conditions throughout the infusion and post-infusion period. For patients at acute risk of hypertensive crisis evaluate the benefit and risks of withholding anti-hypertensive medicine. *Hypersensitivity reactions including anaphylaxis:* Anaphylaxis has been reported. Hypersensitivity may be difficult to distinguish from IRRs. If a hypersensitivity reaction is suspected during infusion, stop the infusion and permanently discontinue Gazyvaro. Patients with known IgE mediated hypersensitivity to obinutuzumab must not be treated. TLS: TLS has been reported – see Dosage & Administration for suggested prophylaxis. Renal function, potassium, and uric acid values in patients at risk should be carefully monitored during initial days of treatment. Neutropenia: Severe and life-threatening neutropenia including febrile neutropenia has been reported and more frequently in patients with renal impairment (CrCl <50 mL/min). Patients with neutropenia should be closely monitored with regular laboratory tests until resolution. Treat in accordance with local guidelines and consider administration of granulocyte-colony stimulating factor. Consider dose delays with severe or life threatening neutropenia. For severe and lasting >1 week neutropenia, antimicrobial prophylaxis strongly recommended throughout the treatment period until resolution to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered. Cases of late onset neutropenia (occurring 28 days after treatment end) and prolonged neutropenia (lasting >28 days after treatment end) have also been reported.

Prescribing information: Gazyvaro® ▼ (obinutuzumab) (continued)

Thrombocytopenia: Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after infusion) has been observed during treatment and more frequently in patients with renal impairment (CrCl <50 mL/min). Fatal haemorrhagic events have also been reported in Cycle 1 of treatment. A clear relationship between thrombocytopenia and haemorrhagic events has not been established. Monitor patients closely during the first cycle; perform regular laboratory tests until event resolution, consider dose delays in cases of severe or life-threatening thrombocytopenia. Use of any concomitant therapies which could worsen thrombocytopenia events should be taken into consideration particularly during the first cycle. *Worsening of pre-existing cardiac conditions:* May occur as part of an IRR and can be fatal. Patients with a history of cardiac disease should be monitored closely and hydrated with caution to prevent fluid overload. *Infections:* Do not administer Gazyvaro in the presence of an active infection and exercise caution when considering use in patients with a history of recurring or chronic infections. In patients with both CIRS>6 and CrCl<70 mL/min, an increased incidence and severity of infections was observed. *Hepatitis B reactivation:* HBV reactivation, some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including Gazyvaro. Perform hepatitis B virus screening (including HBsAg and HBcAb-status) before initiating treatment. Patients with active hepatitis B disease should not be treated and those with positive hepatitis B serology should consult liver disease experts before start of treatment and be monitored and managed to prevent hepatitis reactivation. *Progressive Multifocal Leukoencephalopathy (PML):* PML has been reported and PML diagnosis should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. Evaluation of PML includes consultation with a neurologist, brain MRI and lumbar puncture. Treatment should be withheld during investigation of potential PML; permanently discontinued if PML confirmed and 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. Gazyvaro should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Undesirable effects: For full listings please refer to the Gazyvaro SmPC. *Very common/common*: associated with IRRs - associated symptoms were nausea, fatigue, chills, hypotension, pyrexia, vomiting, dyspnea, flushing, hypertension, headache, tachycardia, dizziness and diarrhea. Respiratory and cardiac symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and atrial fibrillation also reported. Additional very common/ common undesirable effects: upper respiratory tract infection, sinusitis, urinary tract infection, nasopharyngitis, oral herpes, rhinitis, pharyngitis, lung infection, influenza, neutropenia including prolonged and late onset neutropenia, thrombocytopenia, anaemia, leukopenia, squamous cell carcinoma of skin, TLS, hyperuricaemia, depression, ocular hyperaemia, cardiac failure, cough, nasal congestion, rhinorrhea, constipation, alopecia, pruritus, night sweats, eczema, dyspepsia, colitis, haemorrhoids. arthralgia, back pain, musculoskeletal chest pain, pain in extremity, bone pain, lymph node pain, dysuria, urinary incontinence, asthenia, chest pain, weight increased. *Serious reactions:* IRRs, TLS, neutropenia, thrombocytopenia, PML, bacterial, fungal and new or re-activated viral infections, severe haemorrhagic events, worsening of pre-existing cardiac conditions; arrhythmias, angina pectoris, acute coronary syndrome, myocardial infarction and heart failure (these events may occur as part of an IRR and can be fatal). Gastro-intestinal perforation *Elderly:* CLL patients aged ≥75 years experienced more serious adverse events leading to death than patients < 75 years. Consult the SmPC in relation to other adverse reactions

Legal Category: POM

Presentation and Basic NHS Costs: 1000mg of obinutuzumab in 40 mL (25 mg/mL) pack of 1 vial: £3,312.00.

Marketing Authorisation Number: EU/1/14/937/001

Marketing Authorisation Holder: Roche Registration Limited,
6 Falcon Way, Welwyn Garden City, AL7 1TW.

GAZYVARO is a registered trade mark.

RXUKMEDI00226

Date of Preparation June 2016

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. 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.

Prescribing information: MABTHERA® (rituximab)

PRESCRIBING INFORMATION: MABTHERA® (rituximab) 1400mg solution for subcutaneous injection and MABTHERA® 100mg & 500mg concentrate for solution for infusion

Please refer to relevant MabThera SmPC for full prescribing information

Indications: Treatment of follicular lymphoma (FL) with chemotherapy in previously untreated patients with stage III-IV FL, or as maintenance therapy in patients responding to induction therapy.

Treatment of CD20-positive diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) in combination with CHOP.

Dosage and Administration MABTHERA® 100mg and 500mg concentrate for solution for infusion (MabThera IV): Administer prepared MabThera as an IV infusion through a dedicated line, with full resuscitation facilities immediately available and under supervision of an experienced healthcare professional. Do not administer as IV push or bolus. Administer antipyretic and antihistaminic premedication before each infusion. Consider glucocorticoid premedication if chemotherapy does not contain glucocorticoid (FL). Monitor closely for onset of cytokine release syndrome (CRS). Severe reactions e.g. severe dyspnoea, bronchospasm or hypoxia require immediate interruption of infusion. Evaluate FL patients for tumour lysis syndrome (TLS). *Follicular lymphoma:* (i) In combination with chemotherapy for previously untreated or relapsed/refractory FL, 375mg/m2 on day 1 of each chemotherapy cycle for up to 8 cycles, (ii) As maintenance in patients responding to induction therapy for previously untreated FL: 375mg/m2 once ever y 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for maximum of 2 years. In relapsed/refractory patients responding to induction therapy: 375mg/m2 once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for maximum of 2 years. *Diffuse large B-cell non- Hodgkin's lymphoma:* In combination with CHOP, 375mg/m2 on day 1 of each chemotherapy cycle for 8 cycles after iv infusion of the glucocorticoid. *First Infusion:* Recommended initial rate is 50mg/h, after 30 minutes this can be escalated in 50mg/h increments every 30 minutes to a maximum of 400mg/h. *Subsequent Infusions:* Initial rate 100mg/h and increased by 100mg/h increments at 30 minute intervals to a maximum of 400mg/h. *Dose adjustments:* No dose reductions of MabThera IV recommended. *Paediatric use:* Safety and efficacy of MabThera IV in children not established.

Dosage and Administration MABTHERA® 1400mg solution for subcutaneous injection (MabThera SC): All patients must receive their first dose of MabThera by intravenous infusion using MabThera IV. The switch to MabThera SC can only occur at the 2nd or subsequent treatment cycles after successfully receiving a full MabThera IV dose. Administer antipyretic and antihistaminic premedication before each injection. Consider glucocorticoid premedication if chemotherapy does not contain glucocorticoid (FL). Administer MabThera SC as a subcutaneous injection into the abdominal wall over approximately 5 minutes, with full resuscitation facilities immediately available and under supervision of an experienced healthcare professional. The MabThera SC dose is 1400mg irrespective of the patient's body surface area. Administer after iv infusion of the glucocorticoid component of chemotherapy where applicable. Follicular lymphoma: (i) In combination with chemotherapy for previously untreated or relapsed/refractory FL, 1400mg on day 1 of each chemotherapy cycle for up to 8 cycles, (ii) As maintenance in patients responding to induction therapy for previously untreated FL: 1400mg once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for maximum 2 years. In relapsed/refractory patients responding to induction therapy: 1400mg once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for maximum 2 years. Diffuse large B-cell non- Hodgkin's lymphoma: In combination with CHOP, 1400mg on day 1 of each chemotherapy cycle for up to 8 cycles. Dose adjustments: No dose reductions of MabThera SC recommended. Paediatric use: Safety and efficacy of MabThera SC in children not established.

Contra-indications: Hypersensitivity to any component of MabThera IV or SC, to murine proteins or hyaluronidase (SC only). Active, severe infections. Severely immunocompromised patients.

Precautions (MabThera IV and SC): Record tradename in the patient record to improve traceability of biological medicinal products. The use of MabThera SC as monotherapy in stage III-IV FL patients who are chemoresistant or in their 2nd or subsequent relapse after chemotherapy not recommended. Patients must successfully receive a full dose of MabThera IV before switching to MabThera SC because the highest risk of administration reaction is generally observed at first cycle. Use extreme caution and closely monitor first MabThera IV infusion when treating patients with > 25x109/L circulating malignant cells or high tumour burden (higher risk of severe CRS). Consider reduced rate or split dose for any infusion where lymphocyte counts >25x109/L. Infusion/ administration-related reactions (IRRs/ARRs) including CRS, tumour lysis syndrome, anaphylactic and hypersensitivity reactions can be observed with both formulations. Severe IRRs with fatal outcome have been reported, characterised by pulmonary events and in some cases included rapid TLS and features of TLS in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms. See relevant MabThera SmPC for full IRR/ARR details. IRRs of all kinds have been observed in 77% of patients treated with MabThera IV. Anaphylaxis and other hypersensitivity reactions have been reported following IV administration of proteins to patients. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Prescribing information: MABTHERA® (rituximab) (continued)

Since hypotension may occur, consider withholding antihypertensive medications prior to giving MabThera. ARRs have been observed in up to 50% of patients treated with MabThera SC, usually occurring within 24 hours of injection and consisting primarily of erythema, pruritus, rash and local cutaneous reactions (LCRs) (pain, swelling, induration, haemorrhage, erythema, pruritus and rash). Most reactions were mild and transient. Observe for ARRs for at least 15 minutes (longer for patients with increased risk of hypersensitivity reactions) after each SC injection. Instruct patient to contact their physician immediately if any severe hypersentivity or CRS symptoms occur any time after administration. Caution in patients with a history of pulmonary insufficiency or pulmonary tumour infiltration. Closely monitor patients with a history of cardiac disease and/or cardiotoxic chemotherapy. Perform regular full blood counts during MabThera therapy. Caution in patients with a history of, or susceptible to, chronic/recurring infection. Cases of fatal hepatitis B reactivation have been reported. Screen all patients for hepatitis B virus (HBV) before initiating MabThera treatment; do not treat patients with active hepatitis B disease. Patients with positive HBV serology should consult a liver specialist and if treated be monitored and managed to prevent HBV reactivation. Monitor for progressive multifocal leukoencephalopathy (PML) and permanently discontinue MabThera if confirmed. Fatal cases have been reported – refer to relevant MabThera SmPC for more information. Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome – permanently discontinue treatment. For safety or efficacy of immunisation – consult relevant MabThera SmPC.

Pregnancy and Lactation: Use effective contraception during and for 12 months following MabThera treatment.

Undesirable effects: Safety profile of MabThera SC is comparable to MabThera IV (excepting local cutaneous reactions LCRs). *MabThera IV common adverse reactions:* MabThera IV infusion related reactions, reported in more than 50% of patients in clinical trials, predominantly during first infusion, usually in first 2 hours; mainly fever, chills and rigors; other symptoms include flushing, angioedema, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, vomiting and tumour pain; accompanied by hypotension and bronchospasm in up to 12% of cases. Incidence of infusion related symptoms decreases substantially with subsequent infusions. Infections: bacterial, viral & fungal infections reported. Haematological adverse events: occurred in a minority of patients and usually mild and reversible. Severe (grade 3 and 4) events: thrombocytopenia, neutropenia, granulocytopenia, severe anaemia. Cardiovascular events: exacerbation of pre-existing cardiac conditions such as angina pectoris or congestive heart failure. Hypotension, hypertension, arrhythmia. *MabThera SC very common adverse reactions:* ARRs, reported in up to 50% of patients in clinical trials, mainly erythema pruritus, rash and LCRs such as pain, swelling and redness, generally mild or moderate (grade 1 or 2) and transient in nature. LCRs most common during the first SC cycle. Severe (grade 3) events: injection site rash and dry mouth. *MabThera IV serious adverse reactions:* Serious infection including hepatitis B reactivation (common). Late neutropenia, pancytopenia, aplastic anaemia. Severe events in patients with prior cardiac condition or cardiotoxic chemotherapy, heart failure, myocardial infarction, cardiac arrythmias. Hearing loss. Severe vision loss. Multi-organ failure. Infusion related reactions, anaphylaxis, tumour lysis syndrome, cytokine release syndrome, serum sickness. Cranial neuropathy, peripheral neuropathy, facial nerve palsy, loss of other senses and progressive multifocal leukoencephalopathy. Renal failure. Bronchospasm, respiratory failure, pulmonary infiltrates, interstitial lung disease. Gastro-intestinal perforation. Severe bullous skin reactions; Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome. Vasculitis. Cases of posterior reversible encephalopathy syndrome / reversible posterior leukoencephalopathy syndrome reported – see relevant SmPC. *Prescribers should consult the relevant SmPC in relation to other side-effects.*

Legal Category: POM.

Presentations and Basic NHS Costs: 100mg of rituximab in 10mL (10mg/mL) pack of 2 vials: £349.25. 500mg of rituximab in 50mL (10mg/mL) pack of 1 vial: £873.15. 1400mg of rituximab in 11.7 mL (120mg/mL) pack of 1 vial: £1344.65. Marketing Authorisation Numbers: EU/1/98/067/001 (100mg). EU/1/98/067/002 (500mg). EU/1/98/067/003 (1400mg).

Marketing Authorisation Holder: Roche Registration Limited, 6 Falcon Way, Welwyn Garden City, AL7 1TW. MABTHERA is a registered trade mark.

RXUKMEDI00208

Date of Preparation: Feb 2015

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or +44(0)1707 367554.
As MabThera is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number.