Summary of product characteristics

Name of the medicinal product: MabThera 100 mg and MabThera 500 mg concentrate for solution for infusion. **Qualitative and quantitative composition**: Each mL contains 10 mg of rituximab. Each vial contains 100 mg or 500 mg of rituximab. Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures. Excipients with known effects: This medicinal product contains 2.3 mmol (52.6 mg) sodium per 10mL vial. **Pharmaceutical form:** Concentrate for solution for infusion. Clear, colourless liquid. **Therapeutic indications**: MabThera is indicated in adults for the following indications. ***Non-Hodgkin's lymphoma (NHL)***. MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy. MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy. MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. ***Chronic lymphocytic leukaemia (CLL).*** MabThera in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy. **Posology and method of administration**: MabThera should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of MabThera. In patients with non-Hodgkin's lymphoma and CLL, premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy. Posology. It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient, as prescribed. ***Non-Hodgkin's lymphoma.*** *Follicular non-Hodgkin's lymphoma.* Combination therapy**.** The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m^2 body surface area per cycle, for up to 8 cycles. MabThera should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable. Maintenance therapy. *Previously untreated follicular lymphoma.* The recommended dose of MabThera used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years(12 infusions in total). *Relapsed/refractory follicular lymphoma.*The recommended dose of MabThera used as a maintenance treatment for patients with relapsed/ refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years(8 infusions in total). Monotherapy**.** *Relapsed/refractory follicular lymphoma.*The recommended dose of MabThera monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks. For retreatment with MabThera monotherapy for patients who have responded to previous treatment with MabThera monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks. *Diffuse large B cell non-Hodgkin's lymphoma.* MabThera should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma. Dose adjustments during treatment. No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied. ***Chronic lymphocytic leukaemia***. Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after MabThera infusion. Special populations. *Paediatric population.*The safety and efficacy of MabThera in children below 18 years has not been established. No data are available. *Elderly.* No dose adjustment is required in elderly patients (aged >65 years). Method of administration. The prepared MabThera solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest X-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. Mild or moderate infusion-related reactions (IRR) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms. First infusion. The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. Subsequent infusions. *All indications.* Subsequent doses of MabThera can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h. **Contraindications**. Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients. Active, severe infections. Patients in a severely immunocompromised state. **Special warnings and precautions for use:** In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file. Excipients: This medicinal product contains 2.3 mmol (or 52.6 mg) sodium per 10 mL vial. To be taken into consideration by patients on a controlled sodium diet. **Undesirable effects***: Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia(CLL): Summary of the safety profile.*The overall safety profile of MabThera in nonHodgkin's lymphoma and CLL is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy. The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera were IRR reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of MabThera. Infectious events (predominantly bacterial and viral) occurred in approximately 3055 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trials in patients with chronic lymphatic leukaemia (CLL). The most frequent reported or observed serious adverse drug reactions were IRR (including cytokine-release syndrome, tumour-lysis syndrome), infections, cardiovascular events, other serious ADRs reported include hepatitis B reactivation and progressive multifocal leukoencephalopathy (PML). *List of adverse reactions.* The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised hereunder. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known". **ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy: Infections and infestations.** *Very common*: bacterial infections , viral infections , *bronchitis. *Common:* sepsis, *pneumonia, *febrile infection, *herpes zoster, *respiratory tract infection, fungal infections, infections of unknown aetiology, *acute bronchitis, *sinusitis, hepatitis B[1]. *Rare:* serious viral infection[2]. Pneumocystis jirovecci. *Very rare:* PML. **Blood and lymphatic system disorders.** *Very common:* neutropenia, leucopenia, *febrile neutropenia, *thrombocytopenia. *Common:* anaemia, *pancytopenia, *granulocytopenia. *Uncommon:* coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy, *Very rare*: transient increase in serum IgM levels[3]. *Not known:* late neutropenia[3]. **Immune system disorders.** *Very common:* infusion-related reactions[4], angioedema. *Common:* hypersensitivity. *Rare*: anaphylaxis. *Very rare:* tumour lysis syndrome, cytokine release syndrome[4], serum sickness. *Not known*: infusion-related acute reversible thrombocytopenia[4]. **Metabolism and nutrition disorders.** *Common:* hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia. **Psychiatric disorders.** *Uncommon:* depression, nervousness. **Nervous system disorders.** *Common:* paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety *Uncommon:* Dysgeusia. *Very rare:* peripheral neuropathy, facial nerve palsy[5]. *Not known*: cranial neuropathy, loss of other senses[5]. **Eye disorders.** *Common:* lacrimation disorder, conjunctivitis. *Very rare:* severe vision loss[5]. **Ear and labyrinth disorders.** *Common:* tinnitus, ear pain. *Not known:* hearing loss[5]. **Cardiac disorders.** *Common:* *myocardial infarction[4&6], arrhythmia, *atrial fibrillation, tachycardia, *cardiac disorder. *Uncommon:* *left ventricular failure, *supraventricular tachycardia, *ventricular tachycardia, *angina, *myocardial ischaemia, bradycardia. *Rare:* severe cardiac disorders[4&6]. *Very rare*: heart failure[4&6].**Vascular disorders.** *Common:* hypertension, orthostatic hypotension, hypotension. *Very rare:* vasculitis (predominately cutaneous), leukocytoclastic vasculitis. **Respiratory, thoracic and mediastinal disorders.** *Common:* Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis. *Uncommon:* asthma, bronchiolitis obliterans, lung disorder, hypoxia. *Rare:* interstitial lung disease[7].*Very rare:* respiratory failure[4]. *Not known*: lung infiltration. **Gastrointestinal disorders.** *Very common:* nausea. *Common:* vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation. *Uncommon:* abdominal enlargement. *Very rare:* gastro-intestinal perforation[7]. **Skin and subcutaneous tissue disorders.** *Very common:* pruritus, rash, *alopecia. *Common:* urticaria, sweating, night sweats, *skin disorder. *Very rare:* severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)[7]. **Musculoskeletal, connective tissue and bone disorders.** *Common:* hypertonia, myalgia, arthralgia, back pain, neck pain, pain. **Renal and urinary disorders.** *Very rare:* renal failure[4].**General disorders and administration site conditions.** *Very common:* fever, chills, asthenia, headache. *Common:* tumour pain, flushing, malaise, cold syndrome, *fatigue, *shivering, *multi-organ failure[4].*Uncommon:* infusion site pain. **Investigations.** *Very common:* decreased IgG levels. (For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported. [1] Includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL. [2] See also section infection below. [3] See also section haematologic adverse reactions below. [4] See also section infusion-related reactions below. Rarely fatal cases reported. [5] Signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy. [6] Observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions· [7] Includes fatal cases.). The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the MabThera arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia. Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials involving MabThera intravenous formulation, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent intravenous infusions and is <1% of patients by the eighth cycle of MabThera (containing) treatment. Description of selected adverse reactions: ***Infections.*** MabThera induces B-cell depletion in about 70-80% of patients, but was associated with decreased serum immunoglobulins only in a minority of patients. Localized candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm of randomised studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part of a haematopoetic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (PML) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving MabThera in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2% in R-FC vs 0% FC. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive. ***Haematologic adverse reactions.*** In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During MabThera maintenance treatment for up to 2 years, leucopoenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1 %, grade 3/4) and was not different between treatment arms. During MabThera maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1%, grade 3/4) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), pancytopenia (R-FC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below 1x10^9/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below 1x10^9/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with MabThera plus FC. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC 71%). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11% of patients in the R-FC group compared to 9% of patients in the FC group. In studies of MabThera in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months. ***Cardiovascular adverse reactions.*** Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischaemia) in 3% of patients treated with MabThera compared to <1% on observation. In studies evaluating MabThera in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC, 3% FC) and in the relapsed/refractory study (4% R-FC, 4% FC). ***Respiratory system:*** cases of interstitial lung disease, some with fatal outcome have been reported. ***Neurologic disorders.*** During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the first-line study (4% R-FC, 4% FC) and in the relapsed/refractory study (3% R-FC, 3% FC). Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. ***Gastrointestinal disorders.*** Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of Non-Hodgkin's lymphoma (NHL). In the majority of these cases, MabThera was administered with chemotherapy. ***IgG levels.*** In the clinical trial evaluating MabThera maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years). A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown. ***Skin and subcutaneous tissue disorder.*** Toxic Epidermal Necrolysis (Lyell syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely. **Patient subpopulations** *(MabThera monotherapy):* Elderly patients (≥ 65 years): the incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years). Bulky disease: there was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6 % vs. 15.4 %). The incidence of ADRs of any grade was similar in these two groups. Re-treatment: the percentage of patients reporting ADRs upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs). **Patient subpopulations** (*MabThera combination therapy)*:Elderly patients (> 65 years): The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (<65 years), with previously untreated or relapsed/refractory CLL. **Reporting of suspected adverse reactions**: 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. Healthcare professionals are asked to report any suspected adverse reactions. ***Belgium***: Federaal agentschap voor geneesmiddelen en gezondheidsproducten/ Agence fédérale des médicaments et des produits de santé; Afdeling Vigilantie/Division Vigilance; EUROSTATION II, Victor Hortaplein/Place Victor Horta, 40/ 40, B-1060 Brussel/Bruxelles,website/ site internet: www.fagg.be, www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be. ***Luxembourg*** : Direction de la Santé – Division de la Pharmacie et des Médicaments, Villa Louvigny – Allée Marconi, L-2120 Luxembourg, site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html. **Marketing authorisation holder**: Roche Registration Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom. **Marketing authorisation numbers**: For 100mg: EU/1/98/067/001. For 500mg: EU/1/98/067/002. **Date of first autorisation**: 02/06/1998. **Date of latest renewal**: 02/06/2008. **Date of revision of the text**: 4 August 2017. On prescription. Detailed information on this medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu). R.E. Dr Chr. Lenaerts - BE/HAEM/0817/0043- 22/08/2017

Summary of product characteristics

Name of the product: MabThera 1400 mg solution for subcutaneous injection. **Qualitative and quantitative composition:** Each mL contains 120 mg of rituximab. Each vial contains 1400 mg/11.7 mL rituximab. Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures. **Pharmaceutical form:** Solution for injection. Clear to opalescent, colourless to yellowish liquid. Excipients with known effects: This medicinal product contains less than 1mmol sodium per dose, i.e. essentially sodium free. **Therapeutic indications:** MabThera is indicated in adults for ***Non-Hodgkin's lymphoma (NHL).*** MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy. MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy. MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. **Posology and method of administration:** MabThera should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of MabThera. Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy. Posology: The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area. Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation. If patients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered. Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles of treatment. It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and strength is being given to the patient, as prescribed. MabThera subcutaneous formulation is not intended for intravenous administration and should be given via subcutaneous injection only. The 1400 mg strength is intended for subcutaneous use in non-Hodgkin lymphoma (NHL) only. Follicular non-Hodgkin's lymphoma, Combination therapy: The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: first cycle with MabThera intravenous formulation 375 mg/m2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle for up to 8cycles. MabThera should be administered on day 1 of each chemotherapy cycle, after administration of the glucocorticoid component of the chemotherapy if applicable. Maintenance therapy, Previously untreated follicular lymphoma: The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 1400 mg once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (12 administrations in total). Maintenance therapy, Relapsed/refractory follicular lymphoma: The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 1400 mg once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (8 administrations in total). Diffuse large B cell non-Hodgkin's lymphoma: MabThera should be used in combination with CHOP chemotherapy. The recommended dose is: first cycle, MabThera intravenous formulation: 375 mg/m2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle. In total: 8 cycles. MabThera is administered on day 1 of each chemotherapy cycle after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma. Dose adjustments during treatment: No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied. Special populations: *Paediatric population:* the safety and efficacy of MabThera in children below 18 years has not been established. No data are available. *Elderly:* No dose adjustment is required in elderly patients (aged >65 years). Method of administration: *Subcutaneous injection:* MabThera 1400mg subcutaneous formulation should be administered as subcutaneous injection only, over approximately 5 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging. MabThera subcutaneous formulation should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard or areas where there are moles or scars. No data are available on performing the injection in other sites of the body, therefore injections should be restricted to the abdominal wall. During the treatment course with MabThera subcutaneous formulation, other medicinal products for subcutaneous administration should preferably be given at different sites. If an injection is interrupted it can be resumed at the same site or another location may be used, if appropriate. *Intravenous infusion administration:* The Summary of Product Characteristics (SmPC) of MabThera100 mg and 500 mg concentrate for solution for infusion should be referred to for information on dosing instructions and method of administration. **Contraindications:** Hypersensitivity to the active substance or to murine proteins, hyaluronidase. Active, severe infections, patients in a severely immunocompromised state. **Special warnings and precautions for use:** In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file. **Undesirable effects.** Summary of the safety profile. During the development programme, the safety profile of MabThera subcutaneous formulation was comparable to that of the intravenous formulation with the exception of local cutaneous reactions. Local cutaneous reactions, including injection site reactions, were very common in patients receiving MabThera subcutaneous formulation. In the phase 3 SABRINA trial (BO22334), local cutaneous reactions were reported in up to 20% of patients receiving subcutaneous MabThera. The most common local cutaneous reactions in the MabThera subcutaneous arm were injection erythema (13%), injection pain (7%), and injection site oedema (4%). Events seen following subcutaneous administration were mild or moderate, apart from one patient who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) following the first MabThera subcutaneous administration (Cycle 2). Local cutaneous reactions of any grade in the MabThera subcutaneous arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections. ***Adverse reactions reported in MabThera subcutaneous formulation usage.*** The risk of acute administration-related reactions associated with the subcutaneous formulation of MabThera was assessed in two open-label trials involving patients with follicular lymphoma during induction and maintenance (SABRINA BO22334) and during maintenance only (SparkThera BP22333). In SABRINA, severe administration-related reactions (grade≥3) were reported in two patients (2%) following administration of MabThera subcutaneous formulation. These events were Grade 3 injection site rash and dry mouth. In SparkThera, no severe administration-related reactions were reported. ***Adverse reactions reported in MabThera intravenous formulation usage.*** *Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia(CLL):* The overall safety profile of MabThera in nonHodgkin's lymphoma and CLL is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy. The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of MabThera. Infectious events (predominantly bacterial and viral) occurred in approximately 3055 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trial in patients with chronic lymphatic leukaemia (CLL). The most frequent reported or observed serious adverse drug reactions were infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), infections, cardiovascular disorders, other serious ADRs reported include hepatitis B reactivation and progressive multifocal leukoencephalopathy (PML). The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised hereunder. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known". **ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy: Infections and infestations.** *Very common*: bacterial infections , viral infections , +bronchitis. *Common:* sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]. *Rare:* serious viral infection[2]. **Blood and lymphatic system disorders.** *Very common:* neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia. *Common:* anaemia, +pancytopenia, +granulocytopenia. *Uncommon:* coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy, *Very rare*: transient increase in serum IgM levels[3]. *Not known:* late neutropenia[3]. **Immune system disorders.** *Very common:* infusion related reactions[4], angioedema. *Common:* hypersensitivity. *Rare:* anaphylaxis. *Very rare:* tumour lysis syndrome, cytokine release syndrome[4], serum sickness. *Not known*: infusion-related acute reversible thrombocytopenia[4]. **Metabolism and nutrition disorders.** *Common:* hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia. **Psychiatric disorders.** *Uncommon:* depression, nervousness. **Nervous system disorders.** *Common:* paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety *Uncommon:* Dysgeusia. *Very rare:* peripheral neuropathy, facial nerve palsy[5]. *Not known*: cranial neuropathy, loss of other senses[5]. **Eye disorders.** *Common:* lacrimation disorder, conjunctivitis. *Very rare:* severe vision loss[5]. **Ear and labyrinth disorders.** *Common:* tinnitus, ear pain. *Not known:* hearing loss[5]. **Cardiac disorders.** *Common:* +myocardial infarction[4&6], arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder. *Uncommon:* +left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia. *Rare:* severe cardiac disorders[4&6]. *Very rare:* heart failure[4&6].**Vascular disorders.** *Common:* hypertension, orthostatic hypotension, hypotension. *Very rare:* vasculitis (predominately cutaneous), leukocytoclastic vasculitis. **Respiratory, thoracic and mediastinal disorders.** *Common:* Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis. *Uncommon:* asthma, bronchiolitis obliterans, lung disorder, hypoxia. *Rare:* interstitial lung disease[7]. *Very rare:* respiratory failure[4]. *Not known*: lung infiltration. **Gastrointestinal disorders.** *Very common:* nausea. *Common:* vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation. *Uncommon:* abdominal enlargement. *Very rare:* gastro-intestinal perforation[7]. **Skin and subcutaneous tissue disorders.** *Very common:* pruritus, rash, +alopecia. *Common:* urticaria, sweating, night sweats, +skin disorder. *Very rare:* severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)[7]. **Musculoskeletal, connective tissue and bone disorders.** *Common:* hypertonia, myalgia, arthralgia, back pain, neck pain, pain. **Renal and urinary disorders.** *Very rare:* renal failure[4].**General disorders and administration site conditions.** *Very common:* fever, chills, asthenia, headache. *Common:* tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi-organ failure[4].*Uncommon:* infusion site pain. **Investigations.** *Very common:* decreased IgG levels. (For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported. [1] Includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL. [2] See also section infection below. [3] See also section haematologic adverse reactions below. [4] See also section infusion-related reactions below. Rarely fatal cases reported. [5] Signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy. [6] Observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions [7] Includes fatal cases.). The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the MabThera-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia. Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials involving MabThera intravenous formulation, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent intravenous infusions and is <1% of patients by the eighth cycle of MabThera (containing) treatment. Description of selected adverse reactions: ***Infections.*** MabThera induces B-cell depletion in about 70-80% of patients, but was associated with decreased serum immunoglobulins only in a minority of patients. Localized candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm of randomised studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part of a haematopoetic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (PML) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving MabThera in combination with cytotoxic chemotherapy. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive. ***Haematologic adverse reactions.*** In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During MabThera maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1%, grade 3/4) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88% vs. CHOP 79%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported. In studies of MabThera in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months. ***Cardiovascular adverse reactions.*** Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischaemia) in 3% of patients treated with MabThera compared to <1% on observation. In studies evaluating MabThera in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease ***Respiratory system:*** cases of interstitial lung disease, some with fatal outcome have been reported. ***Neurologic disorders.*** During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period. Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. ***Gastrointestinal disorders.*** Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of Non-Hodgkin's lymphoma (NHL). In the majority of these cases, MabThera was administered with chemotherapy. ***IgG levels.*** In the clinical trial evaluating MabThera maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years). ***Skin and subcutaneous tissue disorder.*** Toxic Epidermal Necrolysis (Lyell syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely. **Patient subpopulations** *(MabThera monotherapy):* Elderly patients (≥ 65 years): the incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years). Bulky disease: there was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6 % vs. 15.4 %). The incidence of ADRs of any grade was similar in these two groups. Re-treatment: the percentage of patients reporting ADRs upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs). **Reporting of suspected adverse reactions**: 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. Healthcare professionals are asked to report any suspected adverse reactions. ***Belgium***: Federaal agentschap voor geneesmiddelen en gezondheidsproducten/ Agence fédérale des médicaments et des produits de santé; Afdeling Vigilantie/Division Vigilance; EUROSTATION II, Victor Hortaplein/Place Victor Horta, 40/ 40, B-1060 Brussel/Bruxelles,website/ site internet: www.fagg.be, www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be. ***Luxembourg*** : Direction de la Santé – Division de la Pharmacie et des Médicaments, Villa Louvigny – Allée Marconi, L-2120 Luxembourg, site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html. **Marketing authorisation holder**: Roche Registration Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom. **Marketing authorisation numbers**: EU/1/98/067/003. **Date of first autorisation**: 02/06/1998. **Date of latest renewal**: 02/06/2008. **Date of revision of the text**: 4 August 2017. On prescription. Detailed information on this medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu). R.E. Dr Chr. Lenaerts - BE/HAEM/0817/0044 - 22/08/2017

Summary of product characteristics

Name of the product: MabThera 1600 mg solution for subcutaneous injection. **Qualitative and quantitative composition:** Each mL contains 120 mg of rituximab. Each vial contains 1600 mg/ 13.4 mL rituximab. Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine lightchain and heavychain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures. Excipients with known effects: This medicinal product contains less than 1mmol sodium per dose, i.e. essentially sodium free. **Pharmaceutical form:** Solution for injection. Clear to opalescent, colourless to yellowish liquid. **Therapeutic indications:** MabThera is indicated in adults in combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia (CLL). Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including MabThera or patients refractory to previous MabThera plus chemotherapy. **Posology and method of administration:** MabThera should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an antipyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of MabThera. Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoidcontaining chemotherapy. Posology The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1600 mg irrespective of the patient's body surface area. Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation. If patients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered. Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles of treatment. It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and strength is being given to the patient, as prescribed. MabThera subcutaneous formulation is not intended for intravenous administration and should be given via subcutaneous injection only.The 1600 mg strength is intended for subcutaneous use in CLL only. Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before administration with MabThera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome. The recommended dosage of MabThera in combination with chemotherapy for previously untreated and relapsed/refractory patients is: MabThera intravenous formulation 375 mg/m^2 body surface area administered on day 0 of the first cycle of treatment followed by MabThera subcutaneous formulation injected at a fixed dose of 1600 mg per cycle, on day 1 of each subsequent cycle (in total: 6 cycles). The chemotherapy should be given after MabThera administration. Dose adjustments during treatment No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied. Special populations *Paediatric population* The safety and efficacy of MabThera in children below 18 years has not been established. No data are available. *Elderly* No dose adjustment is required in elderly patients (aged >65 years). Method of administration *Subcutaneous injections* MabThera 1600 mg subcutaneous formulation should be administered as subcutaneous injection only, over approximately 7 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging. MabThera subcutaneous formulation should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard or areas where there are moles or scars. No data are available on performing the injection in other sites of the body, therefore injections should be restricted to the abdominal wall. During the treatment course with MabThera subcutaneous formulation, other medicinal products for subcutaneous administration should preferably be given at different sites. If an injection is interrupted it can be resumed at the same site or another location may be used, if appropriate. *Intravenous infusion administration* The Summary of Product Characteristics (SmPC) of MabThera 100 mg and 500 mg concentrate for solution for infusion should be referred to for information on dosing instructions and method of administration. **Contraindications:** Hypersensitivity to the active substance or to murine proteins, hyaluronidase. Active, severe infections, patients in a severely immunocompromised state. **Special warnings and precautions for use:** In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file. **Undesirable effects.** Summary of the safety profile. During the development programme, the safety profile of MabThera subcutaneous formulation was comparable to that of the intravenous formulation with the exception of local cutaneous reactions. Local cutaneous reactions including injection site reactions were very common in patients receiving MabThera subcutaneous formulation. In the NHL phase 3 trial SABRINA (BO22334), local cutaneous reactions were reported in up to 20% of patients receiving subcutaneous MabThera. The most common local cutaneous reactions in the MabThera subcutaneous arm were injection site erythema (13%), injection site pain (7%), and injection site oedema (4%). Events seen following subcutaneous administration were mild or moderate, apart from one patient who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) following the first MabThera subcutaneous administration (Cycle 2). Local cutaneous reactions of any grade in the MabThera subcutaneous arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections. Similar events were observed in the CLL SAWYER trial (BO25341) and were reported in up to 42% of patients in the MabThera subcutaneous arm. Most common local cutaneous reactions were injection site erythema (26%), injection site pain (16%), and injection site swelling (5%).Two patients in SAWYER trial who experienced Grade 3 local cutaneous reactions (injection site erythema, injection site pain and injection site swelling). ***Adverse reactions reported in MabThera subcutaneous formulation usage.*** The risk of acute administrationrelated reactions associated with the subcutaneous formulation of MabThera was assessed in three clinical trials: SparkThera and SABRINA (the two trials in NHL) and SAWYER the CLL trial. In trial SABRINA, severe administrationrelated reactions (grade≥3) were reported in two patients (2%) following administration of MabThera subcutaneous formulation . These events were Grade 3 injection site rash and dry mouth. In trial SparkThera, no severe administrationrelated reactions were reported. In SAWYER (BO25341), severe administrationrelated reactions (Grade ≥3) were reported in four patients (5%) following MabThera subcutaneous administration. These events were Grade 4 thrombocytopenia and Grade 3 anxiety, injectionsite erythema and urticaria. ***Adverse reactions reported in MabThera intravenous formulation usage.*** *Experience from nonHodgkin's lymphoma and chronic lymphocytic leukaemia:* The overall safety profile of MabThera in nonHodgkin's lymphoma and CLL is based on data from patients from clinical trials and from postmarketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy. The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera were infusionrelated reactions which occurred in the majority of patients during the first infusion. The incidence of infusionrelated symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of MabThera. Infectious events (predominantly bacterial and viral) occurred in approximately 3055 % of patients during clinical trials in patients with NHL and in 3050 % of patients during clinical trial in patients with CLL. The most frequent reported or observed serious adverse drug reactions were: Infusionrelated reactions (including cytokinerelease syndrome, tumourlysis syndrome), infections, cardiovascular disorders, other serious ADRs reported include hepatitis B reactivation and PML. The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). The ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated, are listed under "not known". **ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy: Infections and infestations.** *Very common*: bacterial infections , viral infections , °bronchitis. *Common:* sepsis, °pneumonia, °febrile infection, °herpes zoster, °respiratory tract infection, fungal infections, infections of unknown aetiology, °acute bronchitis, °sinusitis, hepatitis B[1]. *Rare:* serious viral infection[2]. **Blood and lymphatic system disorders.** *Very common:* neutropenia, leucopenia, °febrile neutropenia, °thrombocytopenia. *Common:* anaemia, °pancytopenia, °granulocytopenia. *Uncommon:* coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy, *Very rare*: transient increase in serum IgM levels[3]. *Not known:* late neutropenia[3]. **Immune system disorders.** *Very common:* infusion related reactions[4], angioedema. *Common:* hypersensitivity. *Rare:* anaphylaxis. *Very rare:* tumour lysis syndrome, cytokine release syndrome[4], serum sickness. *Not known*: infusion-related acute reversible thrombocytopenia[4]. **Metabolism and nutrition disorders.** *Common:* hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia. **Psychiatric disorders.** *Uncommon*: depression, nervousness. **Nervous system disorders.** *Common:* paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety *Uncommon:* Dysgeusia. *Very rare:* peripheral neuropathy, facial nerve palsy[5]. *Not known*: cranial neuropathy, loss of other senses[5]. **Eye disorders.** *Common:* lacrimation disorder, conjunctivitis. *Very rare:* severe vision loss[5]. **Ear and labyrinth disorders.** *Common:* tinnitus, ear pain. *Not known:* hearing loss[5]. **Cardiac disorders.** *Common:* °myocardial infarction[4&6], arrhythmia, °atrial fibrillation, tachycardia, °cardiac disorder. *Uncommon:* °left ventricular failure, °supraventricular tachycardia, °ventricular tachycardia, °angina, °myocardial ischaemia, bradycardia. *Rare:* severe cardiac disorders[4&6]. *Very rare*: heart failure[4&6].**Vascular disorders.** *Common:* hypertension, orthostatic hypotension, hypotension. *Very rare:* vasculitis (predominately cutaneous), leukocytoclastic vasculitis. **Respiratory, thoracic and mediastinal disorders.** *Common:* Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis. *Uncommon:* asthma, bronchiolitis obliterans, lung disorder, hypoxia. *Rare:* interstitial lung disease[7].*Very rare:* respiratory failure[4]. *Not known*: lung infiltration. **Gastrointestinal disorders.** *Very common:* nausea. *Common:* vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation. *Uncommon:* abdominal enlargement. *Very rare:* gastro-intestinal perforation[7]. **Skin and subcutaneous tissue disorders.** *Very common:* pruritus, rash, °alopecia. *Common:* urticaria, sweating, night sweats, °skin disorder. *Very rare:* severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)[7]. **Musculoskeletal, connective tissue and bone disorders.** *Common:* hypertonia, myalgia, arthralgia, back pain, neck pain, pain. **Renal and urinary disorders.** *Very rare:* renal failure[4].**General disorders and administration site conditions.** *Very common:* fever, chills, asthenia, headache. *Common:* tumour pain, flushing, malaise, cold syndrome, °fatigue, °shivering, °multi-organ failure[4].*Uncommon:* infusion site pain. **Investigations.** *Very common:* decreased IgG levels. 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Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent intravenous infusions and is <1% of patients by the eighth cycle of MabThera (containing) treatment. Description of selected adverse reactions: ***Infections.*** MabThera induces B-cell depletion in about 70-80% of patients, but was associated with decreased serum immunoglobulins only in a minority of patients. Localized candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm of randomised studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part of a haematopoetic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (PML) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving MabThera in combination with cytotoxic chemotherapy. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive. ***Haematologic adverse reactions.*** In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During MabThera maintenance treatment for up to 2 years, leucopoenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1 %, grade 3/4) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopoenia (RCHOP 88% vs. CHOP 79%, RFC 23% vs. FC 12%), grade 3/4 neutropenia (RCVP 24% vs. CVP 14%; RCHOP 97% vs. CHOP 88%, RFC 30% vs. FC 19% in previously untreated CLL), grade 3/4 pancytopenia (RFC 3% vs. FC 1% in previously untreated CLL) were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies with MabThera intravenous formulation in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with RFC neutropenia was prolonged (defined as neutrophil count remaining below 1x10^9/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below 1x10^9/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with MabThera plus FC.There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported. In the CLL firstline study, Binet stage C patients experienced more adverse events in the RFC arm compared to the FC arm (RFC 83% vs. FC 71%). In the relapsed/refractory CLL study grade 3/4 thrombocytopenia was reported in 11% of patients in the RFC group compared to 9% of patients in the FC group. In studies of MabThera in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months. ***Cardiovascular adverse reactions.*** Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3% of patients treated with MabThera compared to <1% on observation. In studies evaluating MabThera in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the RCHOP group (14 patients, 6.9%) as compared to the CHOP group (3 patients, 1.5%). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or preexisting respiratory and cardiovascular disease. No difference between the RCHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease. In CLL, the overall incidence of grade 3 or 4 cardiac disorders was low both in the firstline study (4% RFC, 3% FC) and in the relapsed/refractory study (4% RFC, 4% FC). ***Respiratory system.*** Cases of interstitial lung disease, some with fatal outcome have been reported. ***Neurologic disorders.*** During the treatment period (induction treatment phase comprising of RCHOP for at most eight cycles), four patients (2 %) treated with RCHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the followup period. In CLL, the overall incidence of grade 3 or 4 nervous system disorders was low both in the firstline study (4% RFC, 4% FC) and in the relapsed/refractory study (3% RFC, 3% FC). Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. ***Gastrointestinal disorders.*** Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of NonHodgkin's lymphoma (NHL). In the majority of these cases, MabThera was administered with chemotherapy. ***IgG levels.*** In the clinical trial evaluating MabThera maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years). ***Skin and subcutaneous tissue disorder.*** Toxic Epidermal Necrolysis (Lyell Syndrome) and StevensJohnson syndrome, some with fatal outcome, have been reported very rarely. **Patient subpopulations** *(MabThera monotherapy):* Elderly patients (≥ 65 years): The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years). Bulky disease: There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6 % vs. 15.4 %). The incidence of ADRs of any grade was similar in these two groups. Retreatment: The percentage of patients reporting ADRs upon retreatment with further courses of MabThera was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs). **Patient subpopulations** – (MabThera combination therapy) Elderly patients (≥ 65 years) . The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (<65 years), with previously untreated or relapsed/refractory CLL. **Reporting of suspected adverse reactions**: 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. Healthcare professionals are asked to report any suspected adverse reactions. ***Belgium***: Federaal agentschap voor geneesmiddelen en gezondheidsproducten/ Agence fédérale des médicaments et des produits de santé; Afdeling Vigilantie/Division Vigilance; EUROSTATION II, Victor Hortaplein/Place Victor Horta, 40/ 40, B-1060 Brussel/ Bruxelles,website/ site internet: www.fagg.be, www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be. ***Luxembourg*** : Direction de la Santé – Division de la Pharmacie et des Médicaments, Villa Louvigny – Allée Marconi, L-2120 Luxembourg, site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html. **Marketing authorisation holder**: Roche Registration Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom. **Marketing authorisation numbers**: EU/1/98/067/004. **Date of first autorisation**: 02/06/1998. **Date of latest renewal**: 02/06/2008. **Date of revision of the text**: 4 August 2017. On prescription. Detailed information on this medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu). R.E. Dr Chr. Lenaerts - BE/HAEM/0817/0045 - 24/08/2017

▼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. **NAME OF THE MEDICINAL PRODUCT:** Gazyvaro 1.000 mg concentrate for solution for infusion. **QUALITATIVE AND QUANTITATIVE COMPOSITION:** One vial of 40 mL concentrate contains 1.000 **mg obinutuzumab, corresponding to a concentration before dilution of 25 mg/mL.** Obinutuzumab is a Type II humanised anti-CD20 monoclonal antibody of the IgG1 subclass derived by humanisation of the parental B-Ly1 mouse antibody and produced in the Chinese Hamster Ovary cell line by recombinant DNA technology. **PHARMACEUTICAL FORM:** Concentrate for solution for infusion. Clear, colourless to slightly brownish liquid. **THERAPEUTIC INDICATIONS:** Chronic Lymphocytic Leukaemia (CLL): Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy. 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 follicular lymphoma. Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. **POSOLOGY AND METHOD OF ADMINISTRATION:** Gazyvaro should be administered under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available. **Posology.** *Prophylaxis and premedication for tumour lysis syndrome (TLS).* Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 10^9/L) and/or renal impairment (CrCl <70 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 treatment such as urate oxidase (e.g. rasburicase), starting 12-24 hours prior to start of Gazyvaro infusion as per standard practice. Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate. *Prophylaxis and premedication for infusion related reactions (IRRs):* 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. List 1: Premedication to be administered before Gazyvaro infusion to reduce the risk of infusion related reactions in patients with CLL and FL. *List 1: Day of treatment cycle, patients requiring premedication, premedication, administration.* **Cycle 1, D1 for CLL and FL**, All patients: intravenous corticosteroid[1](mandatory for CLL, recommended for FL). Administration: completed at least 1 hour prior to Gazyvaro infusion. Oral analgesic/anti-pyretic[2]. Administration: at least 30 minutes before Gazyvaro infusion. Anti-histaminic medicine[3]. Administration: at least 30 minutes before Gazyvaro infusion. **Cycle 1, D2 for CLL only,** All patients: intravenous corticosteroid[1](mandatory). Administration : completed at least 1 hour prior to Gazyvaro infusion. Oral analgesic/anti-pyretic[2]. Administration: at least 30 minutes before Gazyvaro infusion. Anti-histaminic medicine[3]. Administration: at least 30 minutes before Gazyvaro infusion. **All subsequent infusions for CLL and FL,** Patients with no IRR during the previous infusion: Oral analgesic/anti-pyretic[2]. Administration: at least 30 minutes before Gazyvaro infusion. Patients with an IRR (Grade 1 or 2) with the previous infusion: Oral analgesic/anti-pyretic[2]. Administration: at least 30 minutes before Gazyvaro infusion. Anti-histaminic medicine[3]. Administration: at least 30 minutes before Gazyvaro infusion. Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x 10^9/L prior to next treatment: intravenous corticosteroid[1]. Administration: completed at least 1 hour prior to Gazyvaro infusion. Oral analgesic/anti-pyretic[2]. Administration: at least 30 minutes before Gazyvaro infusion. Anti-histaminic medicine[3]. Administration: 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. *1.000* 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 medication if given at least 60 minutes prior to Gazyvaro, in which case additional IV corticosteroid as premedication is not required. Dose:* **CLL, in combination with chlorambucil**. For patients with CLL the recommended dose of Gazyvaro in combination with chlorambucil is shown in List 2.Cycle 1: The recommended dose of Gazyvaro in combination with chlorambucil is 1,000 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 1,000 mg administered on Day 1 of each cycle. *List 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, D1:** 100 mg. **Cycle 1, D2 (or D1 continued):** 900 mg. **Cycle 1 , D8:** 1.000 mg. **Cycle 1, D15:** 1.000 mg. **Cycles 2-6, D1:** 1.000 mg. *Duration of treatment.* Six treatment cycles, each of 28 day duration. *Delayed or missed doses.* If a planned dose of Gazyvaro is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval for Gazyvaro should be maintained between doses. **Follicular lymphoma (FL)**.For patients with FL, the recommended dose of Gazyvaro in combination with chemotherapy is shown in list 3. Patients with previously untreated follicular lymphoma *Induction (in combination with chemotherapy[4])*. Gazyvaro should be administerd with chemotherapy as follows: Six 28-day cycles in combination with bendamustine[2] 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 (CHOP or CVP or bendamustine) should continue to receive Gazyvaro 1,000 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 bendamustine[2])*. Gazyvaro should be administered in six 28-day cycles in combination with bendamustine[2]. *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 1,000 mg as single agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first). *List 3.* Dose of Gazyvaro to be administered during induction treatment, followed by maintenance treatment: *Cycle, day of treatment, dose of Gazyvaro.* **Cycle 1, D1:** 1.000 mg. **Cycle 1 , D8:** 1.000 mg. **Cycle 1, D15:** 1.000 mg. **Cycles 2-6 or 2-8, D1:** 1.000 mg. **Maintenance:** Every two months for two years or until disease progression (whichever occurs first): 1.000mg. *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). *Delayed or missed doses* If a planned dose of Gazyvaro is missed, it should be administered as soon as possible; do not omit it or wait until the next planned dose. If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, requiring delay of treatment, these doses should be given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1. During maintenance, maintain the original dosing schedule for subsequent doses. *Dose modifications during treatment (all indications)* No dose reductions of Gazyvaro are recommended. For management of symptomatic adverse events (including IRRs). **Special populations.** *Elderly.* No dose adjustment is required in elderly patients. *Renal impairment.* No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance [CrCl] 3089 mL/min). The safety and efficacy of Gazyvaro has not been established in patients with severe renal impairment (CrCl < 30 mL/min). *Hepatic impairment.* The safety and efficacy of Gazyvaro in patients with impaired hepatic function has not been established. No specific dose recommendations can be made. *Paediatric population.* The safety and efficacy of Gazyvaro in children and adolescents aged below 18 years has not been established. No data are available. **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. Instructions on the rate of infusion are shown in List 4-5. List 4: CLL: Standard infusion rate in the absence of infusion related reactions/hypersensitivity and recommendations in case an IRR occurred with previous infusion *Cycle, day of treatment, rate of infusion 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"..* **Cycle 1, D1 (100 mg):** administer at 25 mg/hr over 4 hours. Do not increase the infusion rate. **Cycle 1, D2 (or D1 continued) (900mg):** If no IRR occurred 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. 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. **Cycle 1, D8 (1.000mg)/ Cycle 1, D15 (1.000mg)/ Cycles 2-6, D1 (1.000mg):** 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. 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. List 5: Follicular lymphoma: Standard infusion rate in the absence of infusion related reactions/hypersensitivity and recommendations in case an IRR occurred with previous infusion *Cycle, day of treatment, rate of infusion 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".* **Cycle 1, D1 (1.000mg):** 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. **Cycle 1, D8 (1.000mg)/ Cycle 1, D15 (1.000mg)/ Cycle 2-6 or 2-8, D1 (1.000mg)/ Maintenance** [Every 2 months for 2 years or until disease progression (whichever occurs first)]: 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. 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. 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 List 4-5). 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 12 (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 List 4-5). For CLL patients receiving the Day 1 (Cycle 1) dose split over the two days, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file. Based on a subgroup analysis in previously untreated follicular lymphoma, the efficacy in FLIPI low risk (0-1) patients is currently inconclusive. A therapy choice for these patients should carefully consider the overall safety profile of Gazyvaro plus chemotherapy and the patient-specific situation. **UNDESIRABLE EFFECTS: Summary of the safety profile.** The adverse drug reactions (ADRs) described in this section were identified during induction, maintenance and follow up for indolent Non-Hodgkin lymphoma (iNHL) including FL; treatment and follow up for CLL in the three pivotal clinical studies: BO21004/CLL11 (N=781): Patients with previously untreated CLL, BO21223/GALLIUM (N=1390): Patients with previously untreated iNHL (86% of the patients had FL), GAO4753g/GADOLIN (N=392): Patients with iNHL (81% of the patients had FL) who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. These trials investigated Gazyvaro in combination with chlorambucil for CLL and with bendamustine, CHOP or CVP followed by Gazyvaro maintenance therapy for iNHL. The studies BO21223/GALLIUM and GAO4753g/GADOLIN enrolled patients with iNHL including FL. Therefore, in order to provide the most comprehensive safety information, the analysis of ADRs presented in the following has been performed on the entire study population (i.e. iNHL). List 6 summarises the ADRs of the pivotal studies (BO21004/CLL11, BO21223/GALLIUM GAO4753g/GADOLIN) that occurred at a higher incidence (difference of ≥ 2%) compared to the relevant comparator arm in at least one pivotal study in: Patients with CLL receiving Gazyvaro plus chlorambucil compared with chlorambucil alone or rituximab plus chlorambucil (study BO21004/CLL11), Patients with previously untreated iNHL receiving Gazyvaro plus chemotherapy (bendamustine, CHOP, CVP) followed by Gazyvaro maintenance in patients achieving a response, compared to rituximab plus chemotherapy followed by rituximab maintenance in patients achieving a response (study BO21223/GALLIUM), Patients with iNHL who had no response to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen receiving Gazyvaro plus bendamustine, followed by Gazyvaro maintenance in some patients, compared to bendamustine alone (study GAO4753g/GADOLIN). The incidences presented in List 6 (all grades and Grades 3-5) are the highest incidence of that ADR reported from any of the three studies. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. *List 6* **Summary of ADRs reported with a higher incidence (difference of ≥2% versus the comparator arm) in patients[#] receiving Gazyvaro + chemotherapy*** *Frequency, All Grades Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)Grades 3-5[†] Grades 3-5[†] Gazyvaro + chemotherapy* (CLL, iNHL) followed by Gazyvaro maintenance (iNHL)* **Infections and infestations.** Very common, all grades: Upper respiratory tract infection, sinusitis[§], , urinary tract infection, pneumonia[§] herpes zoster[§]. Common, all grades: Oral herpes, rhinitis, pharyngitis, lung infection, influenza nasopharyngitis. Common, grades 3-5†: Urinary tract infection, pneumonia, lung infection, upper respiratory tract infection, sinusitis, herpes zoster. Uncommon, grades 3-5†: Nasopharyngitis, rhinitis, influenza, oral herpes. **Neoplasms benign, malignant and unspecified (incl cysts and polyps).** Common, all grades: squamous cell carcinoma of skin. Common, grades 3-5†: squamous cell carcinoma of skin. **Blood and lymphatic system disorders.** Very common, all grades: Neutropenia[§], thrombocytopenia, anaemia, leukopenia. Very common, grades 3-5†: neutropenia, thrombocytopenia. Common, all grades: Lymph node pain. Common, grades 3-5†: anaemia, leukopenia. **Metabolism and nutrition disorders.** Common, all grades: Tumour lysis syndrome, hyperuricaemia, hypokalaemia Common, grades 3-5†: Tumour lysis syndrome, hypokalaemia. Uncommon, grades 3-5†: hyperuricaemia. **Nervous system disorders.** Very common, all grades: Headache. Uncommon, grades 3-5†, Headache. **Psychiatric disorders. Very common, all grades: Insomnia.** Common, all grades: depression, anxiety. Uncommon, grades 3-5†: Insomnia, depression, anxiety.. **Eye disorders.** Common, all grades: Ocular hyperaemia. **Cardiac disorders.** Common, all grades: atrial fibrillation, cardiac failure. Common, grades 3-5†: Atrial fibrillation, cardiac failure. **Vascular disorders.** Common, all grades: hypertension. Common, grades 3-5†: hypertension. **Respiratory, thoracic and mediastinal disorders.** Very common, all grades: Cough[§]. Common, all grades: Nasal congestion, rhinorrhoea, oropharyngeal pain. Uncommon, grades 3-5†: Cough, oropharyngeal pain. **Gastrointestinal disorders.** Very common, all grades: Diarrhea, constipation[§]. Common, all grades: Dyspepsia, colitis, haemorrhoids. Common, grades 3-5†: diarrhea, colitis. Uncommon, grades 3-5†: Constipation, haemorrhoids. **Skin and subcutaneous tissue disorders.** Very common, all grades: Alopecia, pruritis. Common, all grades: Night sweats, eczema. Uncommon, grades 3-5†: Pruritus, night sweats. **Musculoskeletal and connective tissue disorders.** Very common, all grades: Arthralgia[§], back pain.. Common, all grades: Musculoskeletal chest pain, pain in extremity, bone pain. Uncommon, grades 3-5†: Arthralgia, back pain, musculoskeletal chest pain, bone pain. **Renal and Urinary disorders.** Common, all grades: Dysuria, urinary incontinence. Uncommon, grades 3-5†: Dysuria, urinary incontinence. **General disorders and administration site conditions.** Very common, all grades: pyrexia, asthenia. Common, all grades: chest pain. Common, grades 3-5†: Pyrexia, asthenia. Uncommon, grades 3-5†: Chest pain. **Investigations.** Common, all grades: white blood cell count decreased, neutrophil count decreased, weight increased. Common, grades 3-5†: white blood cell count decreased, neutrophil count decreased. **Injury poisoning and procedural complications.** Very common, all grades: infusion related reactions. Very common, grades 3-5†: infusion related reactions. [#]with a higher incidence (difference of ≥ 2% between the treatment arms). Only the highest frequency observed in the trials is reported (based on studies BO21004/previously untreated CLL, BO21223/previously untreated advanced iNHL and GAO4753g/rituximab refractory iNHL), [†] No Grade 5 adverse reactions have been observed with a difference of ≥ 2% between the treatment arms, * Chemotherapy: Chlorambucil in CLL; bendamustine, CHOP, CVP in iNHL including FL, [§] observed also during maintenance treatment with at least 2% higher incidence in Gazyvaro arm (BO21223). In study GAO4753g/GADOLIN, patients in the bendamustine arm received 6 months of induction treatment only, whereas after the induction period, patients in the Gazyvaro plus bendamustine arm continued with Gazyvaro maintenance treatment. During the maintenance period in study GAO4753g/GADOLIN, the most common adverse reactions were cough (15%), upper respiratory infections (12%), neutropenia (11%), sinusitis (10%), diarrhoea (8%), infusion related reactions (8%), nausea (8%), fatigue (8%), bronchitis (7%), arthralgia (7%), pyrexia (6%), nasopharyngitis (6%), and urinary tract infections (6%). The most common Grade 3-5 adverse reactions were neutropenia (10%), and anaemia, febrile neutropenia, thrombocytopenia, sepsis, upper respiratory tract infection, and urinary tract infection (all at 1%). The profile of adverse reactions in patients with FL was consistent with the overall iNHL population in both studies. **Description of selected adverse reactions.** *The incidences presented in the following sections if referring to iNHL are the highest incidence of that ADR reported from either pivotal study (BO21223/GALLIUM, GAO4753g/GADOLIN).Infusion related reactions (IRRs)* Most frequently reported (≥ 5%) symptoms associated 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. Chronic Lymphocytic Leukaemia The incidence of IRRs was higher in the Gazyvaro plus chlorambucil arm compared to the rituximab plus chlorambucil arm. The incidence of IRRs was 65% with the infusion of the first 1,000 mg of Gazyvaro (20% of patients experiencing a Grade 34 IRR). Overall, 7% of patients experienced an IRR leading to discontinuation of Gazyvaro. The incidence of IRRs with subsequent infusions was 3% with the second 1,000 mg dose and 1% thereafter. No Grade 35 IRRs were reported beyond the first 1,000 mg infusions of Cycle 1. In patients who received the recommended measures for prevention of IRRs as described in section 4.2, a decreased incidence of IRRs of all Grades was observed. The rates of Grade 3-4 IRRs (which occurred in relatively few patients) were similar before and after mitigation measures were implemented. Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma .Grade 3-4 IRRs occurred in 12% of patients. In Cycle 1, the overall incidence of IRRs was higher in patients receiving Gazyvaro plus chemotherapy compared to patients in the comparator arm. In patients receiving Gazyvaro plus chemotherapy, the incidence of IRRs was highest on Day 1 and gradually decreased with subsequent infusions. This decreasing trend continued during maintenance therapy with Gazyvaro alone. Beyond Cycle 1 the incidence of IRRs in subsequent infusions was comparable between the Gazyvaro and the relevant comparator arms. Overall, 3% of patients experienced an infusion related reaction leading to discontinuation of Gazyvaro. *Neutropenia and infections. Chronic Lymphocytic Leukaemia* The incidence of neutropenia was higher in the Gazyvaro plus chlorambucil arm (41%) compared to the rituximab plus chlorambucil arm with the neutropenia resolving spontaneously or with use of granulocyte-colony stimulating factors. The incidence of infection was 38% in the Gazyvaro plus chlorambucil arm and 37% in the rituximab plus chlorambucil arm (with Grade 35 events reported in 12% and 14%, respectively and fatal events reported in < 1% in both treatment arms). Cases of prolonged neutropenia (2% in the Gazyvaro plus chlorambucil arm and 4% in the rituximab plus chlorambucil arm) and late onset neutropenia (16% in the Gazyvaro plus chlorambucil arm and 12% in the rituximab plus chlorambucil arm) were also reported. Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma In the Gazyvaro plus chemotherapy arm, the incidence of Grade 1-4 neutropenia (50%) was higher relative to the comparator arm with an increased risk during the induction period. The incidence of prolonged neutropenia and late onset neutropenia was 3% and 7%, respectively. The incidence of infection was 81% in the Gazyvaro plus chemotherapy arm (with Grade 3-5 events reported in 22% of patients and fatal events reported in 3% of patients). Patients who received G-CSF prophylaxis had a lower rate of Grade 3-5 infections. *Thrombocytopenia and haemorrhagic events* Chronic Lymphocytic Leukaemia. The incidence of thrombocytopenia was higher in the Gazyvaro plus chlorambucil arm (15%) compared to the rituximab plus chlorambucil arm especially during the first cycle. Four percent of patients treated with Gazyvaro plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the Gazyvaro infusion). The overall incidence of haemorrhagic events was similar in the Gazyvaro treated arm and in the rituximab treated arm. The number of fatal haemorrhagic events was balanced between the treatment arms; however, all of the events in patients treated with Gazyvaro were reported in Cycle 1. A clear relationship between thrombocytopenia and haemorrhagic events has not been established. Indolent Non-Hodgkin Lymphoma including Follicular Lymphoma. The incidence of thrombocytopenia was 14%. Thrombocytopenia occurred more frequently in Cycle 1 in the Gazyvaro plus chemotherapy arm. Thrombocytopenia occurring during or 24 hours from end of infusion (acute thrombocytopenia) was more frequently observed in patients in the Gazyvaro plus chemotherapy arm than in the comparator arm. The incidence of haemorrhagic events was similar across all treatment arms. Haemorrhagic events and Grade 3-5 haemorrhagic events occurred in 12% and 5% of patients, respectively. While fatal haemorrhagic events occurred in less than 1% of patients; none of the fatal adverse events occurred in Cycle 1. **Special populations.** *Elderly.* Chronic Lymphocytic Leukaemia. In the pivotal BO21004/CLL11 study, 46% (156 out of 336) of patients with CLL treated with Gazyvaro plus chlorambucil were 75 years or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than those patients < 75 years of age. Indolent Non Hodgkin Lymphoma including Follicular Lymphoma. In the pivotal studies (BO2223/GALLIUM, GAO4753g/GADOLIN) in iNHL, patients 65 years or older experienced more serious adverse events and adverse events leading to withdrawal or death than patients < 65 years of age. *Renal impairment. Chronic Lymphocytic Leukaemia.* In the pivotal BO21004/CLL11 study, 27% (90 out of 336) of patients treated with Gazyvaro plus chlorambucil had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than patients with a CrCl ≥ 50 mL/min (see section 4.2, 4.4 and 5.2). Patients with a CrCl < 30 mL/min were excluded from the study. *Indolent Non Hodgkin Lymphoma including Follicular Lymphoma.* In the pivotal studies (BO21223/GALLIUM, GAO4753g/GADOLIN) in iNHL, 5% (35 out of 698) and 8% (15 out of 194) of patients treated with Gazyvaro, respectively, had moderate renal impairment (CrCL < 50 mL/min). These patients experienced more serious adverse events, adverse events leading to death and adverse events leading to treatment withdrawal than patients with a CrCl ≥ 50 mL/min. Patients with a CrCl < 40 mL/min were excluded from the studies. **Additional safety information from clinical studies experience.** *Progressive multifocal leukoencephalopathy (PML).* PML has been reported in patients treated with Gazyvaro. *Hepatitis B reactivation.* Cases of hepatitis B reactivation have been reported in patients treated with Gazyvaro. *Gastro-Intestinal Perforation.* Cases of gastro-intestinal perforation have been reported in patients receiving Gazyvaro, mainly in iNHL. In the pivotal studies in iNHL up to 1% of patients experienced gastrointestinal perforation. *Worsening of pre-existing cardiac conditions.* Cases of arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with Gazyvaro. These events may occur as part of an IRR and can be fatal. *Laboratory abnormalities.* Transient elevation in liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase) has been observed shortly after the first infusion of Gazyvaro. **Reporting of suspected adverse reactions.** 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. Healthcare professionals are asked to report any suspected adverse reactions. **België/Belgique.** Federaal agentschap voor geneesmiddelen en gezondheidsproducten /Agence fédérale des médicaments et des produits de santé - Afdeling Vigilantie / Division Vigilance - EUROSTATION II, Place Victor Hortaplein, 40/ 40 - B-1060 Brussel/ Bruxelles - Website: www.fagg.be / Site internet: www.afmps.be - e-mail: adversedrugreactions@fagg-afmps.be. **Luxembourg.** Direction de la Santé – Division de la Pharmacie et des Médicaments, Villa Louvigny – Allée Marconi, L-2120 Luxembourg, Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html. **MARKETING AUTHORISATION HOLDER.** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom. **MARKETING AUTHORISATION NUMBER(S):** EU/1/14/937/001. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:** 23/07/2014. **DATE OF REVISION OF THE TEXT:** 18/09/2017. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu. R.E Dr. Chr. Lenaerts – BE/HAEM/0917/0049 – 29/09/2017