24. VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of disease epidemiology

Obinutuzumab (Gazyvaro®) is used to treat chronic lymphocytic leukemia (referred to as CLL) and is intended to prolong the period of time during which the patient is in remission.

In Europe, in 2000-2002, the combined incidence of CLL and another leukemia (small lymphocytic lymphoma) was approximately 5 per 100,000 people (approximately 75% of these patients had CLL). CLL is almost twice as common in men as in women, and its incidence increases with age. The median age for diagnosis of CLL in the US is 72 years of age.

VI.2.2 Summary of treatment benefits

For those patients with previously untreated CLL who are able to tolerate intense chemotherapy, the current accepted treatment of choice is rituximab in combination with chemotherapy (fludarabine and cyclophosphamide). For those patients who are not suitable for fludarabine-based treatment because of other medical conditions or age related problems, the standard treatment in Europe is chlorambucil or rituximab in combination with chlorambucil.

Obinutuzumab increased the time without CLL getting worse (progression-free survival) when it was given with chlorambucil. In the key study in previously untreated patients, the median progression-free survival was 26.7 months in patients who received obinutuzumab and chlorambucil and 11.1 months in those who received chlorambucil alone. Fourteen percent of the patients who received chlorambucil and 76% of patients who received obinutuzumab and chlorambucil were progression-free after one year.

Survival is still being assessed, but information from the key study (in which patients have been followed for 21.6 months on average) suggests that the addition of obinutuzumab to chlorambucil increases the overall survival of CLL patients: the most recent review showed that 9.2% of patients who received obinutuzumab and chlorambucil had died, compared with 20.3% of the patients who received only chlorambucil..

Additional information from this study looking at a larger group of patients treated with obinutuzumab also suggests that progression-free survival is increased in patients given obinutuzumab and chlorambucil compared with those given rituximab and chlorambucil. The median progression-free survival was 26.7 months in patients who received obinutuzumab and chlorambucil and 15.2 months in those who received rituximab and chlorambucil. Sixty-four percent of the patients who received rituximab and chlorambucil and 86% of patients who received obinutuzumab and chlorambucil were progression-free after one year.

Results from this study also suggest that the addition of obinutuzumab to chlorambucil increases the overall survival of CLL patients compared with the addition of rituximab to chlorambucil: the most recent review showed that 8.4% of patients who received obinutuzumab and chlorambucil had died, compared with 12.4% of the patients who received rituximab and chlorambucil. However, it should be noted that these patients have been followed for 19.1 months on average and survival is still being assessed.

VI.2.3 Unknowns relating to treatment benefits

The main study with obinutuzumab was carried out in adult patients who had mild or moderate kidney problems and/or other medical conditions besides their CLL. The information gained from this key study is considered to apply to all patients with previously untreated CLL and other medical conditions making them unsuitable for full dose fludarabine-based therapy.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Infusion-related reactions	The majority of patients treated with obinutuzumab have experienced reactions related to infusion of the drug. These reactions occur mainly during or after the first infusion. Their frequency and severity decrease with later infusions. Reactions reported to date include headache, fever, flushing, chills, feeling sick, shortness of breath, low or high blood pressure, tachycardia (heart beating very fast), nausea, vomiting and diarrhea. Less frequently, some	The risk of infusion-related reactions can be reduced by administration of prophylactic medication (corticosteroids, paracetamol, anti-histamines).In addition, the first infusion of obinutuzumab can be given split over two days: Infusion may be slowed down, or interrupted should severe symptoms occur and appropriate medication given to treat the symptoms. Patients treated with anti-hypertensive medication (drugs that control blood pressure) may have their medication withheld before

Risk	What is known	Preventability
	patients may experience wheezing, difficulty breathing, tight chest, throat irritation, throat and airway swelling and irregular heartbeat. Most reactions have been mild to moderate, but some severe and life-threatening reactions have been reported.	and during infusion
Tumor lysis syndrome	Treatment with obinutuzumab can result in the tumor cells being destroyed very quickly, which can result in adverse effects as the body tries to remove the breakdown products from these cells (potassium, phosphate and uric acid). Tumor lysis syndrome may be serious and can lead to kidney failure.	Drinking plenty of fluids and taking the drug allopurinol 12-24 hours prior to infusion of obinutuzumab is recommended for patients with high circulating white blood cell counts in order to reduce the risk of tumor lysis syndrome.
Low levels of platelets (blood cells which help blood to clot) (Thrombocytopenia}	Some patients have had a significant reduction in the number of platelets in their blood after treatment with obinutuzumab. In most cases this was not serious. However, thrombocytopenia may give rise to hemorrhages (bleeding) which can be fatal.	Low platelet levels cannot be prevented Transfusion of blood products may be required to increase the number of platelets and to reduce the risk of bleeding.

Risk	What is known	Preventability
Low levels of neutrophils (a type of white blood cell) (Neutropenia)	Increased rates of neutropenia have been observed in patients treated with obinutuzumab. Low levels of neutrophils may lead to infections. Most cases of neutropenia in obinutuzumab-treated patients were non-serious and of short duration, although some serious cases associated with infections, some life-threatening, have been reported	Low neutrophil levels cannot be prevented. Patients who experience neutropenia should be closely monitored until neutrophil levels return to normal.
Low levels of neutrophils which first occur after obinutuzumab treatment ends or which last more than a month after treatment ends (Late onset/prolonged neutropenia)	Neutrophil (white blood cell) levels in the blood may fall more than 28 days after treatment has been completed and low neutrophil levels found during treatment may take a long time to return to normal (longer than one month after treatment stops). This may increase the risk of infections, although most infections seen in obinutuzumab-treated patients who experienced delayed or prolonged neutropenia were mild.	The occurrence of late onset or prolonged neutropenia cannot be prevented.

Risk	What is known	Preventability
Delay in return of B-cell lymphocytes (white blood cells which play a major role in the immune system response) to normal levels (Prolonged B-cell depletion)	Lowering the level of B-cell lymphocytes is the intended effect of obinutuzumab. The time taken for B-cell lymphocytes to return to normal levels in the body may be very long (i.e., more than one year). Prolonged depletion of white blood cells could potentially increase the risk from infection, although studies with obinutuzumab have not confirmed this.	Prolonged depletion cannot be prevented, but blood cell levels can be monitored to follow their return to normal.
Infections	White blood cells help the body to fight infection, therefore the removal of B-cells (white blood cells which play a major role in the immune system response) by obinutuzumab and the neutropenia that can occur after obinutuzumab treatment increase the risk of infection. Some infections can be serious or even fatal.	Obinutuzumab should not be given to patients with active infections. The risk of infection can be reduced by good oral hygiene (with dental assessment before treatment if necessary) and avoidance of constipation. Signs or symptoms of infection should receive prompt medical treatment.
Return of hepatitis B in patients who have had hepatitis B in the past (Hepatitis B reactivation)	In patients who have had hepatitis B in the past, treatment with obinutuzumab may increase the risk of the hepatitis B infection coming back. Reactivation of hepatitis B is known to	Return of hepatitis B in patients who have had hepatitis B in the past (Hepatitis B reactivation)

Risk	What is known	Preventability
	occur in patients who undergo chemotherapy and in patients treated with drugs similar to obinutuzumab. The chance of developing an active hepatitis B infection is low, but this can sometimes be serious, or even fatal.	
A very rare and life-threatening viral infection called progressive multifocal leukoencephalopathy (PML)	PML causes brain damage and is almost always fatal or causes severe disability. This disease can occur in cancer patients even if they do not receive anticancer treatment. PML has occurred in patients with cancer treated with drugs similar to obinutuzumab, and one patient treated with obinutuzumab has developed the infection.	PML cannot be prevented but patients can be monitored to detect the condition.
Worsening of heart problems (Cardiac disorders)	Worsening of existing cardiac conditions has been seen in some patients treated with obinutuzumab, although a direct association with obinutuzumab has not been established.	Patients with cardiac disorders should be closely monitored. The amount and rate of fluid administered to prevent tumor lysis syndrome may need to be adjusted in patients with known cardiac disorders to minimize the risk of worsening heart problems.

Important potential risks

Risk	**What is known (*Including reason why it is considered a potential risk)***
Vaccinations may not be effective (Impaired immunization response)	The action of obinutuzumab on white blood cells may reduce the effect of vaccination. No vaccination studies have been performed in patients receiving obinutuzumab.
Development of antibodies against the drug (Immunogenicity)	Patients may develop antibodies against obinutuzumab that could affect their ability to respond to treatment or result in adverse events.
Second primary cancers (Second malignancies)	Patients treated with obinutuzumab may be at increased risk of developing new cancers because of depletion of their white blood cells. The development of new cancers has been seen in some patients treated with obinutuzumab. However, there are other risk factors for the development of second cancers in CLL patients including the underlying disease and advanced age (most CLL patients are elderly).
Hole in the gut (Gastrointestinal perforation)	Patients may be at increased risk for the development of gastrointestinal perforation when treated with obinutuzumab. Cases have been seen in patients treated with obinutuzumab for another type of leukemia (NHL). No cases have been seen in CLL patients treated with obinutuzumab to date, but cases have been seen in CLL patients treated with a similar drug (MabThera®).
Effects on the kidney (Immune-mediated glomerulonephritis)	Effects in the kidney have been seen in monkeys treated with obinutuzumab. These effects are considered to be specific to animals and have not been observed in humans.

Missing information

Risk	What is known
Use in children	Obinutuzumab has not been studied in children.
Use in pregnancy and while breast-feeding	Obinutuzumab has not been studied in women who are pregnant or breast-feeding. Studies in monkeys have not identified any particular risks for pregnant mothers, although infants were born with low levels of white blood cells (which play a major role in the immune system response). Women who are able to become pregnant should use an effective method of birth control for 18 months after treatment with obinutuzumab. If women do receive treatment with obinutuzumab during pregnancy, infants may be born with low levels of white blood cells. Vaccination of these infants with live vaccines should be delayed until the infant's white blood cell levels return to normal. Because it is possible that obinutuzumab may be excreted in human milk, women should be advised not to breast feed during obinutuzumab therapy and for 18 months after treatment with obinutuzumab.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study BO21004: Obinutuzumab + chlorambucil compared to rituximab + chlorambucil or chlorambucil alone in previously untreated CLL patients with comorbidities. 3	Primary: demonstration of clinically relevant statistical superiority in PFS obinutuzumab + Clb compared to rituximab + Clb and Clb alone and RClb compared to Clb in previously untreated CLL patients with comorbidities. Includes secondary objective to evaluate and compare the safety profile of patients.	IRRs (confirmation of decrease in IRRs since protocol amendment introducing split dosing, slow infusion and reinforcing pre-existing risk minimization measures) (complete) Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q1 2014 (Stage 2 analysis CSR) Q3 2022 (Final CSR)
Study BO21005: Obinutuzumab in combination with CHOP versus rituximab and CHOP in previously untreated patients with CD20-positive DLBCL 3	Primary: demonstrate superiority in PFS of obinutuzumab plus chemotherapy vs. rituximab plus chemotherapy in previously untreated DLBCL patients Includes secondary objective to evaluate and compare the safety profiles of patients treated with the combination of obinutuzumab and CHOP with rituximab and CHOP	Thrombocytopenia Late onset and prolonged neutropenia Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q1 2017

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study BO21223: Obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy in previously untreated patients with advanced indolent lymphoma followed by GA101[24] or rituximab maintenance therapy in responders 3	Primary: Efficacy of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in previously untreated advanced follicular lymphoma Includes secondary objective to evaluate and compare the safety profiles between the two arms	Thrombocytopenia Late onset and prolonged neutropenia Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q4 2017
Study MO28543: Obinutuzumab in combination with chemotherapy in patients with previously untreated or relapsed/refractory CLL 3	Primary: To evaluate the safety and tolerability of obinutuzumab alone or in combination with chemotherapy	IRRs	Study ongoing	Q4 2018

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Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study GAO4753g: Obinutuzumab in combination with bendamustine compared with bendamustine in patients with rituximab-refractory indolent NHL 3	To evaluate clinical benefit in terms of PFS of obinutuzumab in combination with bendamustine compared with bendamustine alone in patients with indolent NHL refractory to prior rituximab-containing therapy. Includes secondary objective evaluate and compare the safety profiles of patients treated with bendamustine and obinutuzumab and bendamustine alone.	Thrombocytopenia Prolonged B-cell depletion	Study Ongoing	Q4 2016 (approx.)
Drug Safety Report on hemorrhagic events in the context of thrombocytopenia 3	Evaluation of the incidence, severity and temporal relationship of hemorrhagic events and assessment of relationship with thrombocytopenia	Thrombocytopenia	In preparation	Q1 2015 (latest, for submission within PBRER)

Studies which are a condition of the marketing authorisation

Not applicable.

VI.2.7. Summary of changes to the Risk Management Plan over time

Major Changes to the Risk Management Plan over time

Version	Date (At time of authorization)*	Safety Concerns	Comment
1.0	Evaluated	**Identified Risks** Infusion related reactions Tumor lysis syndrome Thrombocytopenia Neutropenia Late onset and prolonged neutropenia Prolonged B-cell depletion Infections Progressive multifocal leukoencephalopathy Worsening of pre-existing cardiac conditions **Potential Risks** Hepatitis B reactivation Impaired immunization response Immunogenicity Second malignancies GI perforation Immune-mediated glomerulonephritis	
1.1	Under evaluation	Hepatitis B reactivation changed to an identified risk. Use in children and Use in pregnancy and lactation added as missing information	Hepatitis B reactivation is now an identified risk based on cases reported in patients exposed to obinutuzumab.
1.2		-	Minor updates only. No major changes.

*Refers to the date of CHMP positive opinion. Please note, not all versions of the EU RMP are approved by the CHMP.