# EU Risk Management Plan for Truxima®/Blitzima® (rituximab)

| **RMP version to be assessed as part of this application:** | |
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| RMP Version number: | 12.0 |
| Data lock point for this RMP: | 21 October 2024 |
| Date of final sign off: | 26 June 2025 |
| Rationale for submitting an updated RMP: | Updated the safety concerns and additional risk minimisation measures, and deleted specific adverse reaction follow-up questionnaires to align with the reference product, MabThera. |
| Summary of significant changes in this RMP | <u>Part I: Product Overview</u><br>- ATC code updated<br>- Ritemvia deleted following withdrawal of brand name on 21 June 2021<br>- Additional monitoring status updated to 'No' since Truxima/Blitzima has been removed from the list of medicinal products under additional monitoring<br><u>Part II: Safety specification</u><br>- Module SI: Epidemiology section deleted as it is no longer required for biosimilar medicinal products in line with the integrated format EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2.<br>- Module SV: Post-authorisation exposure updated with the data lock point of 30 September 2023 as per the most recent PBRER.<br>- Modules SVII.2 and SVIII: Removal of the important identified risks 'Hepatitis B virus (HBV) reactivation' and 'Hypogammaglobulinaemia', important potential risks 'Malignancy', 'Impact on cardiovascular disease', 'Relapse of GPA/MPA', and 'Administration route error', and missing information 'Use during pregnancy or lactation' and 'Long-term use in GPA/MPA patients'<br><u>Part III: Pharmacovigilance plan</u><br>- Routine pharmacovigilance activities - has been updated with removal of specific adverse reaction follow-up questionnaires |

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| | Part V: Risk minimisation measures<br>- Safety concerns updated as per Part II<br>- Additional risk minimisation measures (Guide for healthcare professionals, patient guide, and physician information) removed<br>Part VII: Annexes<br>- Annex 4: Specific adverse reaction follow-up questionnaires removed<br>- Annex 6: Additional risk minimisation measures (Physician information and Patient information) removed<br>- Annex 7: Other supporting data has been updated in accordance with removal of the important identified risks 'Hepatitis B virus (HBV) reactivation' and 'Hypogammaglobulinaemia', important potential risks 'Malignancy', 'Impact on cardiovascular disease', 'Relapse of GPA/MPA', and 'Administration route error', and missing information 'Use during pregnancy or lactation' and 'Long-term use in GPA/MPA patients' |
| **Other RMP versions under evaluation:** Not applicable | |
| RMP Version number: | - |
| Submitted on: | - |
| Procedure number: | - |
| **Details of the currently approved RMP:** | |
| Version number: | 12.0 |
| Approved with procedure: | EMA/VR/0000244743 |
| Date of approval (opinion date): | 19 June 2025 |
| **QPPV name:** | Oliver Wiedemann |
| **QPPV oversight declaration:** | *The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.* |

Note: Throughout this document, symbols indicating proprietary names (®, ™) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

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## LIST OF ABBREVIATIONS

| Term | Explanation |
|---|---|
| ADA | Anti-drug antibody |
| ADCC | antibody-dependent cellular cytotoxicity |
| AE | Adverse event |
| ADR | Adverse drug reaction |
| AFL | Advanced follicular lymphoma |
| AIDS | Acquired immunodeficiency syndrome |
| AUC | Area under curve |
| CD20 | human B-lymphocyte-restricted differentiation antigen, Bp35 |
| CDC | complement-dependent cytotoxicity |
| cf. | compared with |
| CHOP | cyclophosphamide, doxorubicin, vincristine, prednisolone |
| CI | Confidence interval |
| CLL | chronic lymphocytic leukaemia |
| CSR | Clinical study report |
| CT-P10 | Biosimilar rituximab |
| CVP | cyclophosphamide, vincristine, prednisone |
| DLBCL | Diffuse large B-cell lymphoma |
| DMARD | disease-modifying anti-rheumatic drug |
| EPAR | European public assessment report |
| EU | European Union |
| FL | Follicular lymphoma |
| GPA | granulomatosis with polyangiitis |
| GVP | good pharmacovigilance practices |
| HBcAb | Hepatitis B core antibody |
| HBsAb | Hepatitis B surface antibody |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HIV | Human immunodeficiency virus |
| IRR | Infusion-related reaction |
| IV | intravenous |

| Term | Explanation |
|---|---|
| JC | John Cunningham (virus) |
| L | litre |
| $m^2$ | Square metres |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligrams |
| mL | millilitre |
| MPA | microscopic polyangiitis |
| NHL | non-Hodgkin's lymphoma |
| PD | pharmacodynamic |
| PhV | pharmacovigilance |
| PK | pharmacokinetic |
| PML | Progressive multifocal leukoencephalopathy |
| PRES | Posterior reversible encephalopathy syndrome |
| PSUR | Periodic safety update report |
| PV | Pemphigus vulgaris |
| PY | Patient-year |
| RA | Rheumatoid arthritis |
| RMP | Risk management plan |
| RR | Relative risk |
| SLE | systemic lupus erythematosus |
| SmPC | Summary of product characteristics |
| TB | Tubercle bacillus/tuberculosis |
| TEAE | Treatment emergent adverse events |
| TLS | tumour lysis syndrome |
| TNF | tumour necrosis factor |
| UK | United Kingdom |
| US | United States |

# PART I: PRODUCT(S) OVERVIEW

## Table 1 Part I.1: Product Overview

| | |
|---|---|
| **Active substance(s) (INN or common name)** | Rituximab |
| **Pharmacotherapeutic group(s) (ATC Code)** | Antineoplastic agents, monoclonal antibodies and antibody drug conjugates (L01FA01) |
| **Marketing Authorisation Holder or Applicant** | CELLTRION Healthcare Hungary Kft. |
| **Medicinal products to which this RMP refers** | 2 |
| **Invented name(s) in the European Economic Area (EEA)** | Truxima®, 1)<br>Blitzima®, 2) |
| **Marketing authorisation procedure** | Centralised |
| **Brief description of the product** | **Chemical class**<br>Truxima/Blitzima (biosimilar rituximab) is a recombinant chimeric mouse/human glycosylated IgG1 monoclonal antibody. |
| | **Summary of mode of action**<br>Truxima/Blitzima binds to CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35) on B-lymphocytes, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal cells. The CD20 antigen is also expressed on the B-cell in >95% of all non-Hodgkin's lymphoma (NHL) patients. After binding to the CD20 antigen on the cell surface, Truxima/Blitzima is believed to exert its therapeutic effect by promoting B cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and induction of apoptosis. |
| | **Important information about its composition**<br>The antibody is produced by mammalian (Chinese hamster ovary DG44) cell suspension culture.<br>Truxima/Blitzima is a biosimilar medicinal product. The reference product is MabThera®. The antibody has been engineered by development of DNA designed to encode a protein that showed 100% sequence coverage to the reference product's heavy and light chains by peptide mapping. |
| **Hyperlink to the Product Information** | CTD Module 1.3.1 |

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| **Indication(s) in the EEA** | **Current:**<br>Non-Hodgkin's lymphoma (NHL)<br><br>Truxima/Blitzima is indicated for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma in combination with chemotherapy.<br><br>Truxima/Blitzima maintenance therapy is indicated for the treatment of adult follicular lymphoma patients responding to induction therapy.<br><br>Truxima/Blitzima monotherapy is indicated for treatment of adult patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.<br><br>Truxima/Blitzima is indicated for the treatment of adult patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.<br><br>Truxima/Blitzima in combination with chemotherapy is indicated for the treatment of paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL).<br><br>Chronic lymphocytic leukaemia (CLL)<br><br>Truxima/Blitzima in combination with chemotherapy is indicated for the treatment of adult 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 Truxima/Blitzima or patients refractory to previous Truxima/Blitzima plus chemotherapy.<br><br>Rheumatoid arthritis [3)]<br><br>Truxima in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) |

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| | including one or more tumour necrosis factor (TNF) inhibitor therapies.<br><br>Truxima has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.<br><br><u>Granulomatosis with polyangiitis and microscopic polyangiitis</u><br><br>Truxima/Blitzima, in combination with glucocorticoids, is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).<br><br>Truxima/Blitzima, in combination with glucocorticoids, is indicated for the induction of remission in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA.<br><br><u>Pemphigus vulgaris</u><br><br>Truxima/Blitzima is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris (PV). |
| | **Proposed:** Not applicable |
| **Dosage in the EEA** | **Current:**<br><u>Non-Hodgkin's lymphoma</u><br><br>*Follicular non-Hodgkin's lymphoma*<br><br>Combination therapy:<br>The recommended dose of rituximab 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.<br>Rituximab should be administered on Day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable.<br><br>Maintenance therapy:<br>Previously untreated follicular lymphoma |

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| | The recommended dose of rituximab 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).<br><br>Relapsed/refractory follicular lymphoma<br>The recommended dose of rituximab 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).<br><br>Monotherapy:<br>Relapsed/refractory follicular lymphoma<br>The recommended dose of rituximab 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.<br><br>For retreatment with rituximab monotherapy for patients who have responded to previous treatment with rituximab 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.<br><br>*Adult Diffuse large B cell non-Hodgkin's lymphoma*<br><br>Rituximab 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 rituximab have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin’s lymphoma.<br><br><u>Chronic lymphocytic leukaemia</u> |

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| | The recommended dosage of rituximab 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 rituximab infusion.<br><br>Rheumatoid arthritis<br><br>A course of rituximab consists of two 1000 mg intravenous infusions. The recommended dosage of rituximab is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later.<br><br>The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns.<br><br>Available data suggest that clinical response is usually achieved within 16 - 24 weeks of an initial treatment course. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.<br><br>Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)<br><br>*Adult induction of remission*<br>The recommended dosage of rituximab for induction of remission therapy in adult patients with GPA and MPA is 375 mg/m$^2$ body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).<br><br>*Adult maintenance treatment*<br>Following induction of remission with rituximab, maintenance treatment in adult patients with GPA and MPA should be initiated no sooner than 16 weeks after the last rituximab infusion.<br><br>Following induction of remission with other standard of care immunosuppressants, rituximab maintenance treatment should be initiated during the 4 week period that follows disease remission. |

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| | Rituximab should be administered as two 500 mg IV infusions separated by two weeks, followed by a 500 mg IV infusion every 6 months thereafter. Patients should receive rituximab for at least 24 months after achievement of remission (absence of clinical signs and symptoms). For patients who may be at higher risk for relapse, physicians should consider a longer duration of rituximab maintenance therapy, up to 5 years.<br><br>Pemphigus vulgaris<br><br>The recommended dosage of rituximab for the treatment of pemphigus vulgaris is 1000 mg administered as an IV infusion followed two weeks later by a second 1000 mg IV infusion in combination with a tapering course of glucocorticoids.<br><br>*Maintenance treatment*<br>A maintenance infusion of 500 mg IV should be administered at months 12 and 18, and then every 6 months thereafter if needed, based on clinical evaluation.<br><br>*Treatment of relapse*<br>In the event of relapse, patients may receive 1000 mg IV. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation.<br><br>Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion.<br><br>Special populations<br><br>*Paediatric population*<br><br>Non-Hodgkin's lymphoma<br>In paediatric patients from ≥ 6 months to < 18 years of age with previously untreated, advanced stage CD20 positive DLBCL/BL/BAL/BLL, rituximab should be used in combination with systemic Lymphome Malin B (LMB) chemotherapy. The recommended dosage of rituximab is 375mg/$m^2$ BSA, administered as an IV infusion. No rituximab dose adjustments, other than by BSA, are required. |

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| | Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)<br>*Induction of remission*<br>The recommended dosage of rituximab for induction of remission therapy in paediatric patients with severe, active GPA or MPA is 375 mg/m$^2$ BSA, administered as an IV infusion once weekly for 4 weeks. |
| | **Proposed:** Not applicable |
| **Pharmaceutical form(s) and strengths** | **Current:**<br>Truxima/Blitzima 100 mg and 500 mg concentrate for solution for infusion<br><br>Each vial contains 100 mg or 500 mg of rituximab in 10 mL or 50 mL, respectively<br><br>Each mL of concentrate contains 10 mg of rituximab |
| | **Proposed:** Not applicable |
| **Is/will the product be subject to additional monitoring in the EU?** | No |

1) Truxima marketing authorisation granted via EU Centralised procedure
2) Blitzima: a duplicate marketing authorisation has been granted via Centralised procedure that limits the indication to NHL, CLL, GPA/MPA, and PV, due to patent restrictions
3) Rheumatoid arthritis indication is applicable for Truxima only.

# PART II: SAFETY SPECIFICATION

## PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

According to the Guidance on the format of the risk management plan (RMP) in the EU – in integrated format EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2, this part of the Risk Management Plan (RMP) is not required for biosimilar medicinal products.

# PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

**Toxicity**

- **Repeat-Dose Toxicity**

  *Monkey (Cynomolgus Monkey):*

  *3 animals/sex/group, doses of CT-P10 and MabThera® at 0 and 20 mg/kg IV on Day 1, 8, 15, 22, and Day 29 (Day 36 for male) (Study No. ZIP0003).*

  Death in 1/3 males and 1/3 females at 20 mg/kg MabThera®

  There were two deaths during the treatment period amongst animals receiving MabThera® (1 female on Day 29 [fifth dose], 1 male on Day 36 [sixth dose]).

  The two decedents showed lower than group-mate serum concentrations of MabThera® at all time-points on Day 22 indicating that there was a heightened immune response observed in these animals. However, neutralising anti-drug antibody titres were of a similar magnitude across all animals testing positive, including the two decedents.

  The sudden deaths seen in animals receiving MabThera® may have been attributable to intravenous bolus administration. The recommendations are that MabThera® should not be administered as a bolus but by intravenous infusion. There were no deaths associated with CT-P10 treatment.

  MabThera® has been in clinical use for more than 21 years. Since administration of rituximab is via intravenous infusion in humans, it is reasonable to infer that these events are not relevant to the treatment of humans.

  Depletion of B-cells

  The main finding related to this 8-week repeat-dose toxicity study was that the total number of B-cells in peripheral blood was greatly reduced in both male and female monkeys. This is consistent with the expected pharmacological activity of rituximab. Furthermore, the total number of B-cells in the spleen, lymph node and bone marrow were also reduced in both male and female monkeys, with the greatest reductions being seen in the lymph node.

  The depletion of B-cells with rituximab was reported in the MabThera® clinical development programme.

  Potential increased susceptibility to infection and an inadequate response to vaccination due to B-cell depletion.

  Lower lymphocyte, neutrophil, eosinophil and basophil counts

  A treatment related decrease in total and differential white blood cell counts was observed for animals receiving CT-P10 or MabThera® compared to the control and/or pre-treatment values on Day 3, approximately 48 hours after the first dose, with the effect predominantly due to lower lymphocyte counts (0.42-0.5 X control for both sexes receiving CT-P10 or MabThera®). During Week 4, lower lymphocyte, neutrophil, eosinophil and basophil counts were recorded for females receiving CT-P10 or MabThera® (total counts 0.63 X and 0.5 X

control for CT-P10 and MabThera® respectively). For males, the only the significant difference from controls was lower neutrophil counts for animals receiving MabThera® (0.48 X control).

Potential increased susceptibility to infection

Decrease in serum cholesterol concentration in female and lower plasma phosphorus concentrations in male

Cholesterol values statistically significantly lower than controls were observed in female monkeys receiving CT-P10 in Week 7 (0.78 x control), and to a lesser extent in females receiving MabThera® in Week 7 (0.86 x control). At Week 8, statistically significantly lower plasma phosphorus concentrations compared with control were observed for male animals receiving CT-P10 or MabThera® attaining at a level of 0.79 x control (p=0.05), and 0.61 x control (p=0.01), respectively.

The blood chemistry findings in animals administered either CT-P10 or MabThera® including lower than control cholesterol and phosphorus were similar to each other and were slight or apparent in only one sex. This finding is of no toxicological significance to humans.

Weight change in kidney and thymus

At the end of the treatment period kidney weights higher than controls were observed for females receiving either CT-P10 or MabThera® (1.2 x control and 1.3 x control, respectively). The effect was not observed in males. Slightly high individual thymus weights were observed in animals receiving CT-P10 or MabThera® compared with the control range, attaining statistical significance for both sexes receiving MabThera®.

MabThera® has been used safely in the clinic for the last 21 years. Since the organ weight changes for CT-P10 and MabThera® were similar, these observations are unlikely to be relevant to the treatment of humans.

Histopathological change in mesenteric lymph node and spleen

At the end of the treatment period, histopathological changes considered to be related to treatment with CT-P10 were seen in the mesenteric lymph nodes and spleens of males and females. Changes related to treatment with MabThera® were also seen in the mesenteric lymph nodes of males and females but only in the spleens of males.

MabThera® has been used safely in the clinic for the last 21 years. Since these histopathological changes for CT-P10 and MabThera® were similar, these observations are unlikely to be relevant to the treatment of humans.

- **Reproductive and Developmental Toxicity**
  Reproductive toxicology studies comparing CT-P10 and MabThera® have not been performed because they are not required according to EU guidance on biosimilar products (CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010).

- **Genotoxicity/Carcinogenicity**
  Genotoxicity/carcinogenicity studies comparing CT-P10 and MabThera® have not been performed because they are not required according to EU guidance on biosimilar products

(CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010).

**Safety pharmacology**

- **Cardiotoxicity**
  There was no evidence of cardiotoxicity in any of the repeat-dose studies performed as part of non-clinical investigations. Consequently, no non-clinical cardiotoxicity studies have been conducted with CT-P10.
- **General Safety Pharmacology**
  No specific safety pharmacology studies were performed. Safety end-points were incorporated into the monkey repeat-dose toxicity study (Study No. ZIP0003). This approach is compatible with CHMP guidance on similar biological medicinal products containing monoclonal antibodies, which states that safety pharmacology studies are not routinely required (CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010).

**Other toxicity-related information or data**

- **Mechanisms for Drug Interactions**
  On the basis of the specificity of rituximab, the extensive clinical experience with the reference product and the lack of documented drug-drug interactions, no non-clinical studies pertinent to drug interaction have been conducted.
- **Juvenile Toxicity Studies**
  Juvenile toxicity studies were not performed in line with the CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues, Feb 2006 and CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010, 18 November 2010).

## PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Truxima/Blitzima (CT-P10) has been developed as a biosimilar medicinal product. The reference product is MabThera® (rituximab). MabThera® is authorised in the EU both as a formulation for intravenous infusion and as a formulation for subcutaneous injection. Truxima/Blitzima has only been developed as a formulation for intravenous administration.

MabThera® for intravenous infusion is authorised in the EU for use with the following indications: rheumatoid arthritis in adults; non-Hodgkin's lymphoma in both adults and children; chronic lymphocytic leukaemia in adults; granulomatosis with polyangiitis in both adults and children; microscopic polyangiitis in both adults and children; and pemphigus vulgaris in adults.

Clinical development studies with Truxima/Blitzima have been conducted in rheumatoid arthritis and oncology indications. The clinical development programme comprises six studies, including maintenance studies. The data-lock point that was used to generate the clinical data presented in this risk management plan is 18 October 2019. As of this date, there are a total of five clinical studies which has been completed and one has been terminated.

The completed studies comprise

- a randomised, controlled comparison of the pharmacokinetics, efficacy and safety of patients with rheumatoid arthritis treated with up to two courses of CT-P10 or MabThera® (Study CT-P10 1.1)
- an open-label maintenance study in which eligible subjects from Study CT-P10 1.1 were treated with CT-P10 for a total cumulative observation interval in both studies for each subject of up to 104 weeks (Study CT-P10 1.3)
- a randomised, controlled comparison of the pharmacokinetics, efficacy and safety of patients with rheumatoid arthritis treated with up to three courses of CT-P10 or MabThera® or Rituxan® (Study CT-P10 3.2), and
- a randomised, controlled comparison of the pharmacokinetics, efficacy and safety of patients with advanced follicular lymphoma treated with up to eight cycles of cyclophosphamide, vincristine, and prednisone with CT-P10 or Rituxan®, followed by up to 12 cycles of CT-P10 or Rituxan® (Study CT-P10 3.3)
- a randomised, controlled comparison of the efficacy and safety of patients with low tumour burden follicular lymphoma treated with four cycles of CT-P10 or Rituxan® at weekly intervals, followed by up to 6 cycles of CT-P10 or Rituxan® at two-monthly intervals and 6 cycles of CT-P10 at two-monthly intervals (Study CT-P10 3.4).

There was, in addition, an open-label, non-comparative pilot study, which was terminated prematurely due to the inability to recruit patients with diffuse large B-cell lymphoma after one subject had been entered (Study CT-P10 1.2).

All databases for the estimation of exposure were locked before 18 October 2019.

Exposure data are presented for completed studies (the randomised, controlled study in rheumatoid arthritis (Study CT-P10 1.1), the open-label maintenance study in rheumatoid arthritis (Study CT-P10 1.3), the randomised, controlled study in rheumatoid arthritis (Study CT-P10 3.2), the randomised, controlled study in advanced follicular lymphoma (Study CT-P10 3.3), and the randomised, controlled study in low tumour burden follicular lymphoma (Study CT-P10 3.4)). The

exposure data presented do not include data from Study CT-P10 1.2. This was an open-label pilot study that intended to recruit 10 patients with diffuse large B-Cell lymphoma. However, this study was terminated prematurely after only one patient had been enrolled, due to recruitment difficulties at the study centre. The patient enrolled had a partial response after Cycle 2 and before Cycle 3; this patient was treated until Cycle 3 over a period of approximately six weeks.

Rituximab by intravenous infusion for the treatment of rheumatoid arthritis is administered in courses consisting of two infusions, which are infused two weeks apart. The timing of administration of the second and subsequent courses of treatment is dependent on the response of the disease to treatment with the previous course, and will therefore vary from patient to patient. Rituximab for the treatment of follicular non-Hodgkin's lymphoma is administered in combination with chemotherapy for up to eight cycles for induction, and then every 2 months thereafter for maintenance for up to two years. These methods of administration do not lend themselves easily to the estimation of exposure to treatment as might, for example, the administration of a daily tablet. The clinical trial exposure estimates presented below should be understood to represent the completed duration of observation of patients treated in clinical trials, which is the most relevant metric with respect to exposure to risk from rituximab infusions.

**Rheumatoid arthritis**

A total of 392 subjects with rheumatoid arthritis were exposed to CT-P10 and 262 to the reference rituximab products (Table 2). A total of 372 subjects received at least one dose of CT-P10 in Study CT-P10 1.1 and in another randomised blinded trial, Study CT-P10 3.2. At the beginning of the extension study period of Study CT-P10 3.2, 109 patients who received the reference products during the main study period were switched to treatment with CT-P10. A total of 58 patients received at least one dose of CT-P10 in maintenance Study CT-P10 1.3. Twenty subjects who received the reference product in Study CT-P10 1.1 were subsequently treated with CT-P10 in the open-label maintenance Study CT-P10 1.3.

One hundred and ninety-five (195) subjects with rheumatoid disease have received CT-P10 for more than 12 months. A total of 129 subjects have been treated with CT-P10 after having previously received the reference product. The dataset includes subjects that have been treated for rheumatoid arthritis for up to 30 months; 64 subjects were treated with CT-P10 for between 18 months and 24 months, and one subject for between 24 months and 30 months.

The gender distribution of subjects with rheumatoid disease exposed to CT-P10 favours women (339 females compared with 53 males), but all adult age groups are almost equally represented in the dataset.

**Non-Hodgkin's lymphoma**

A total of 303 subjects each with Non-Hodgkin's lymphoma (advanced follicular lymphoma (AFL) and low tumour burden follicular lymphoma (LTBFL)) were exposed to CT-P10 and 198 to the reference rituximab product (Table 2). All exposure estimates are derived from Study CT-P10 3.3 and Study CT-P10 3.4. A total of 79 subjects were exposed to CT-P10 for more than 36 months and 5 subjects for more than 48 months.

**Table 2 Part II.SIII.1: Duration of Exposure**

| INDICATION: Rheumatoid Arthritis (Randomised, Blinded Trial Population) | | |
|---|---|---|
| | CT-P10 1000mg | |

| | Total | | CT-P10 only | | Switched from Rituximab Reference Product 1000mg* | | Rituximab Reference Product 1000mg | |
|---|---|---|---|---|---|---|---|---|
| **Duration of exposure** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| Total | 372 | 135345 | 263 | 116311 | 109 | 19034 | 262 | 105168 |
| <= 6 months | 117 | 18481 | 21 | 2326 | 96 | 16155 | 16 | 1507 |
| >6 months - <= 12 months | 72 | 21999 | 59 | 19120 | 13 | 2879 | 118 | 40129 |
| >12 months - <= 18 months | 146 | 72013 | 146 | 72013 | 0 | 0 | 102 | 47547 |
| >18 months - <= 24 months | 36 | 22081 | 36 | 22081 | 0 | 0 | 25 | 15173 |
| >24 months - <= 30 months | 1 | 771 | 1 | 771 | 0 | 0 | 1 | 812 |
| >30 months - <= 36 months | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Study CT-P10 1.1 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 52 weeks after the reference product treatment.

Note. month = 30.4375 days

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) – [Date of First Exposure to Treatment] + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

| **INDICATION: Non-Hodgkin's Lymphoma (Randomised, Blinded Trial Population)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **CT-P10 375mg/m$^2$** | | | | | | **Rituximab Reference Product 375mg/m$^2$** | |
| | **Total** | | **CT-P10 only** | | **Switched from Rituximab Reference Product*** | | | |
| **Duration of exposure** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| Total | 303 | 245258 | 200 | 193765 | 103 | 51493 | 198 | 137283 |
| <= 6 months | 10 | 900 | 9 | 787 | 1 | 113 | 5 | 412 |
| >6 months - <= 12 months | 24 | 7670 | 5 | 1275 | 19 | 6395 | 7 | 1667 |
| >12 months - <= 18 months | 55 | 24950 | 3 | 1313 | 52 | 23637 | 106 | 44436 |
| >18 months - <= 24 months | 28 | 18141 | 5 | 3338 | 23 | 14803 | 8 | 4945 |
| >24 months - <= 30 months | 66 | 54115 | 58 | 47570 | 8 | 6545 | 10 | 8149 |
| >30 months - <= 36 months | 41 | 40447 | 41 | 40447 | 0 | 0 | 5 | 5026 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| >36 months - <= 42 months | 51 | 60345 | 51 | 60345 | 0 | 0 | 35 | 41588 |
| >42 months - <= 48 months | 23 | 30918 | 23 | 30918 | 0 | 0 | 14 | 18878 |
| >48 months - <= 54 months | 5 | 7772 | 5 | 7772 | 0 | 0 | 8 | 12182 |

Study CT-P10 3.3 and Study CT-P10 3.4

*: Subjects switched to CT-P10 at 13 months after the reference product treatment from Study CT-P10 3.4.

Note. month = 30.4375 days

Subject time (days) = ([Date of End of Study Participation], [Date of End of Study], [Date of First Exposure of Switch - 1] or [Date of Death], whichever is earlier) - [Date of First Exposure to Treatment] + 1
or ([Date of End of Study] or [Date of Death], whichever is earlier) –[Date of First Exposure of Switch] + 1

**INDICATION: Rheumatoid Arthritis (All Trial Population)**

| | **CT-P10 1000mg** | | | | | | **Rituximab Reference Product 1000mg** | |
|---|---|---|---|---|---|---|---|---|
| | **Total** | | **CT-P10 only** | | **Switched from Rituximab Reference Product 1000mg*** | | | |
| **Duration of exposure** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| Total | 392 | 147332 | 263 | 123993 | 129 | 23339 | 262 | 105168 |
| <= 6 months | 126 | 19919 | 21 | 2326 | 105 | 17593 | 16 | 1507 |
| >6 months - <= 12 months | 71 | 20796 | 47 | 15050 | 24 | 5746 | 118 | 40129 |
| >12 months - <= 18 months | 130 | 65718 | 130 | 65718 | 0 | 0 | 102 | 47547 |
| >18 months - <= 24 months | 64 | 40128 | 64 | 40128 | 0 | 0 | 25 | 15173 |
| >24 months - <= 30 months | 1 | 771 | 1 | 771 | 0 | 0 | 1 | 812 |
| >30 months - <= 36 months | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Study CT-P10 1.1, Study CT-P10 1.3 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 80 weeks after the reference product treatment.

Note. month = 30.4375 days

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) - [Date of First Exposure to Treatment] + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

## Table 3 Part II.SIII.2: Age group and Gender

| INDICATION: Rheumatoid Arthritis (Randomised, Blinded Trial Population) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CT-P10 1000mg | | | | | | | | | | | | Rituximab Reference Product 1000mg | | | |
| | Total | | | | CT-P10 only | | | | Switched from Rituximab Reference Product 1000mg* | | | | | | | |
| | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | |
| Age Group (years) | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| 18 - 40 | 7 | 64 | 2939 | 21874 | 6 | 46 | 2771 | 18762 | 1 | 18 | 168 | 3112 | 4 | 41 | 1871 | 16569 |
| 41 - 50 | 20 | 80 | 7683 | 28850 | 12 | 53 | 6266 | 24173 | 8 | 27 | 1417 | 4677 | 14 | 59 | 5363 | 23988 |
| 51 - 60 | 10 | 103 | 3826 | 38061 | 8 | 76 | 3488 | 33219 | 2 | 27 | 338 | 4842 | 13 | 71 | 6077 | 28616 |
| > 60 | 14 | 74 | 5909 | 26203 | 11 | 51 | 5390 | 22242 | 3 | 23 | 519 | 3961 | 5 | 55 | 2025 | 20659 |
| Total | 51 | 321 | 20357 | 114988 | 37 | 226 | 17915 | 98396 | 14 | 95 | 2442 | 16592 | 36 | 226 | 15336 | 89832 |

Study CT-P10 1.1 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 52 weeks after the reference product treatment.

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) - Date of First Exposure to Treatment + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

| INDICATION: Non-Hodgkin's Lymphoma (Randomised, Blinded Trial Population) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CT-P10 375mg/m² | | | | | | | | | | | | Rituximab Reference Product 375mg/m² | | | |
| | Total | | | | CT-P10 only | | | | Switched from Rituximab Reference Product* | | | | | | | |
| | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | |
| Age Group (years) | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| 18 - 40 | 22 | 14 | 19197 | 13988 | 18 | 11 | 17348 | 12740 | 4 | 3 | 1849 | 1248 | 12 | 11 | 7752 | 9350 |
| 41 - 50 | 23 | 34 | 15789 | 30629 | 13 | 22 | 11055 | 24093 | 10 | 12 | 4734 | 6536 | 16 | 19 | 10225 | 13151 |
| 51 - 60 | 37 | 41 | 28782 | 32904 | 24 | 26 | 21789 | 25184 | 13 | 15 | 6993 | 7720 | 25 | 28 | 15431 | 20639 |
| 61 - 70 | 41 | 47 | 31593 | 38572 | 26 | 31 | 25236 | 30077 | 15 | 16 | 6357 | 8495 | 29 | 33 | 18868 | 23543 |
| > 70 | 18 | 26 | 15388 | 18416 | 15 | 14 | 13478 | 12765 | 3 | 12 | 1910 | 5651 | 8 | 17 | 6976 | 11348 |
| Total | 141 | 162 | 110749 | 134509 | 96 | 104 | 88906 | 104859 | 45 | 58 | 21843 | 29650 | 90 | 108 | 59252 | 78031 |

Study CT-P10 3.3 and Study CT-P10 3.4

*: Subjects switched to CT-P10 at 13 months after the reference product treatment from Study CT-P10 3.4.

Subject time (days) = ([Date of End of Study Participation], [Date of End of Study], [Date of First Exposure of Switch - 1] or [Date of Death], whichever is earlier) - [Date of First Exposure to Treatment] + 1
or ([Date of End of Study] or [Date of Death], whichever is earlier) –[Date of First Exposure of Switch] + 1

| INDICATION: Rheumatoid Arthritis (All Trial Population) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CT-P10 1000mg | | | | | | | | | | | | Rituximab Reference Product 1000mg | | | |
| | Total | | | | CT-P10 only | | | | Switched from Rituximab Reference Product 1000mg* | | | | | | | |
| | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | | Subjects (n) | | Subject-time (days) | |
| Age Group (years) | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| 18 - 40 | 9 | 67 | 3282 | 23483 | 6 | 46 | 2771 | 19736 | 3 | 21 | 511 | 3747 | 4 | 41 | 1871 | 16569 |
| 41 - 50 | 20 | 85 | 8343 | 31577 | 12 | 53 | 6926 | 26156 | 8 | 32 | 1417 | 5421 | 14 | 59 | 5363 | 23988 |
| 51 - 60 | 10 | 110 | 4125 | 41668 | 8 | 76 | 3787 | 35037 | 2 | 34 | 338 | 6631 | 13 | 71 | 6077 | 28616 |
| > 60 | 14 | 77 | 5909 | 28945 | 11 | 51 | 5390 | 24190 | 3 | 26 | 519 | 4755 | 5 | 55 | 2025 | 20659 |
| Total | 53 | 339 | 21659 | 125673 | 37 | 226 | 18874 | 105119 | 16 | 113 | 2785 | 20554 | 36 | 226 | 15336 | 89832 |

Study CT-P10 1.1, Study CT-P10 1.3 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 80 weeks after the reference product treatment.

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) - Date of First Exposure to Treatment + 1))
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

## Table 4 Part II.SIII.3: Dose and Number of Administration

| INDICATION: Rheumatoid Arthritis (Randomised, Blinded Trial Population) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CT-P10 1000mg | | | | | | Rituximab Reference Product 1000mg | |
| | Total | | CT-P10 only | | Switched from Rituximab Reference Product 1000mg* | | | |
| **Duration of exposure** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| First Course, 1 infusion | 9 | 860 | 8 | 690 | 1 | 170 | 6 | 487 |
| First Course, 2 infusion | 160 | 33282 | 52 | 14418 | 108 | 18864 | 37 | 10144 |
| Second Course, 1 infusion | 2 | 577 | 2 | 577 | 0 | 0 | 4 | 1196 |
| Second Course, 2 infusion | 80 | 34439 | 80 | 34439 | 0 | 0 | 151 | 57666 |
| Third Course, 1 infusion | 4 | 2108 | 4 | 2108 | 0 | 0 | 0 | 0 |
| Third Course, 2 infusion | 117 | 64079 | 117 | 64079 | 0 | 0 | 64 | 35675 |
| Fourth Course, 1 infusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fourth Course, 2 infusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 372 | 135345 | 263 | 116311 | 109 | 19034 | 262 | 105168 |
| | | | | | | | | |
| Total Cumulative Dose (mg) Mean | 3690.25 | - | 4394.57 | - | 1990.83 | - | 4111.86 | - |
| Total Cumulative Dose (mg) Median | 4000 | - | 4000 | - | 2000 | - | 4000 | - |
| Total Cumulative Dose (mg) Min | 70 | - | 70 | - | 1000 | - | 50 | - |
| Total Cumulative Dose (mg) Max | 6000 | - | 6000 | - | 2000 | - | 6000 | - |

Study CT-P10 1.1 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 52 weeks after the reference product treatment.

Note. month = 30.4375 days

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) – [Date of First Exposure to Treatment] + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

| INDICATION: Non-Hodgkin's Lymphoma (Randomised, Blinded Trial Population) | | | | |
|---|---|---|---|---|
| | CT-P10 375mg/m$^2$ | | | Rituximab Reference Product 375mg/m$^2$ |
| | Total | CT-P10 only | Switched from Rituximab Reference Product* | |

| Number of Administration | Subjects (n) | Subject-time (days) | Subjects (n) | Subject-time (days) | Subjects (n) | Subject-time (days) | Subjects (n) | Subject-time (days) |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 484 | 1 | 16 | 1 | 468 | 2 | 58 |
| 2 | 5 | 1161 | 2 | 226 | 3 | 935 | 2 | 2355 |
| 3 | 4 | 3035 | 3 | 2499 | 1 | 536 | 0 | 0 |
| 4 | 8 | 1984 | 7 | 1751 | 1 | 233 | 9 | 5444 |
| 5 | 1 | 162 | 1 | 162 | 0 | 0 | 3 | 2672 |
| 6 | 102 | 52703 | 5 | 3382 | 97 | 49321 | 7 | 5183 |
| 7 | 2 | 1353 | 2 | 1353 | 0 | 0 | 1 | 166 |
| 8 | 2 | 1542 | 2 | 1542 | 0 | 0 | 6 | 3419 |
| 9 | 4 | 3684 | 4 | 3684 | 0 | 0 | 5 | 5302 |
| 10 | 2 | 1169 | 2 | 1169 | 0 | 0 | 105 | 45815 |
| 11 | 4 | 4259 | 4 | 4259 | 0 | 0 | 6 | 4084 |
| 12 | 4 | 3871 | 4 | 3871 | 0 | 0 | 1 | 501 |
| 13 | 3 | 2865 | 3 | 2865 | 0 | 0 | 1 | 647 |
| 14 | 4 | 3088 | 4 | 3088 | 0 | 0 | 5 | 4282 |
| 15 | 3 | 2972 | 3 | 2972 | 0 | 0 | 1 | 1144 |
| 16 | 101 | 95056 | 101 | 95056 | 0 | 0 | 1 | 1308 |
| 17 | 3 | 3165 | 3 | 3165 | 0 | 0 | 3 | 4059 |
| 18 | 1 | 1473 | 1 | 1473 | 0 | 0 | 1 | 1196 |
| 19 | 2 | 2070 | 2 | 2070 | 0 | 0 | 1 | 890 |
| 20 | 46 | 59162 | 46 | 59162 | 0 | 0 | 38 | 48758 |
| Total | 303 | 245258 | 200 | 193765 | 103 | 51493 | 198 | 137283 |
| | | | | | | | | |
| Total Cumulative Dose (mg) Mean | 8264.88 | - | 10521.78 | - | 3882.55 | - | 7764.70 | - |
| Total Cumulative Dose (mg) Median | 9384.00 | - | 11084.90 | - | 3937.50 | - | 6941.25 | - |
| Total Cumulative Dose (mg) Min | 589.00 | - | 589.00 | - | 685.00 | - | 770.00 | - |
| Total Cumulative Dose (mg) Max | 18315.00 | - | 18315.00 | - | 5352.00 | - | 16233.75 | - |

Study CT-P10 3.3 and Study CT-P10 3.4

*: Subjects switched to CT-P10 at 13 months after the reference product treatment from Study CT-P10 3.4.

Subject time (days) = ([Date of End of Study Participation], [Date of End of Study], [Date of First Exposure of Switch - 1] or [Date of Death], whichever is earlier) - [Date of First Exposure to Treatment + 1 or ([Date of End of Study] or [Date of Death], whichever is earlier) –[Date of First Exposure of Switch] + 1

| **INDICATION: Rheumatoid Arthritis (All Trial Population)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **CT-P10 1000mg** | | | | | | **Rituximab Reference Product 1000mg** | |
| | **Total** | | **CT-P10 only** | | **Switched from Rituximab Reference Product 1000mg*** | | | |
| **Duration of exposure** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| First Course, 1 infusion | 9 | 860 | 8 | 690 | 1 | 170 | 6 | 487 |
| First Course, 2 infusion | 167 | 33164 | 39 | 9995 | 128 | 23169 | 37 | 10144 |
| Second Course, 1 infusion | 3 | 930 | 3 | 930 | 0 | 0 | 4 | 1196 |
| Second Course, 2 infusion | 67 | 30269 | 67 | 30269 | 0 | 0 | 151 | 57666 |
| Third Course, 1 infusion | 4 | 2108 | 4 | 2108 | 0 | 0 | 0 | 0 |
| Third Course, 2 infusion | 141 | 79289 | 141 | 79289 | 0 | 0 | 64 | 35675 |
| Fourth Course, 1 infusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fourth Course, 2 infusion | 1 | 712 | 1 | 712 | 0 | 0 | 0 | 0 |
| Total | 392 | 147332 | 263 | 123993 | 129 | 23339 | 262 | 105168 |
| | | | | | | | | |
| Total Cumulative Dose (mg) Mean | 3800.44 | - | 4687.34 | - | 1992.25 | - | 4111.86 | - |
| Total Cumulative Dose (mg) Median | 4000 | - | 6000 | - | 2000 | - | 4000 | - |
| Total Cumulative Dose (mg) Min | 70 | - | 70 | - | 1000 | - | 50 | - |
| Total Cumulative Dose (mg) Max | 8000 | - | 8000 | - | 2000 | - | 6000 | - |

Study CT-P10 1.1, Study CT-P10 1.3 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 80 weeks after the reference product treatment.

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) - Date of First Exposure to Treatment + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

## Table 5 Part II.SIII.4: Ethnic Origin

| INDICATION: Rheumatoid Arthritis (Randomised, Blinded Trial Population) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CT-P10 1000mg | | | | | | Rituximab Reference Product 1000mg | |
| | Total | | CT-P10 only | | Switched from Rituximab Reference Product 1000mg* | | | |
| **Ethnic Origin** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| White | 230 | 83063 | 160 | 70623 | 70 | 12440 | 173 | 69296 |
| Black | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asian | 32 | 11611 | 27 | 10745 | 5 | 866 | 21 | 7338 |
| Other | 110 | 40671 | 76 | 34943 | 34 | 5728 | 68 | 28534 |
| Unspecified | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 372 | 135345 | 263 | 116311 | 109 | 19034 | 262 | 105168 |

Study CT-P10 1.1 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 52 weeks after the reference product treatment.

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) - Date of First Exposure to Treatment + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

| INDICATION: Non-Hodgkin's Lymphoma (Randomised, Blinded Trial Population) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CT-P10 375mg/m$^2$ | | | | | | Rituximab Reference Product 375mg/m$^2$ | |
| | Total | | CT-P10 only | | Switched from Rituximab Reference Product* | | | |
| **Number of Administration** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| American Indian or Alaska native | 6 | 4659 | 3 | 3170 | 3 | 1489 | 3 | 1265 |
| Asian | 96 | 70487 | 58 | 52864 | 38 | 17623 | 62 | 35618 |
| Black or African American | 2 | 2332 | 2 | 2332 | 0 | 0 | 0 | 0 |
| Hispanic or Latino | 6 | 7400 | 6 | 7400 | 0 | 0 | 3 | 3402 |
| Native Hawaiian or other pacific islander | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| White or Caucasian | 189 | 157808 | 128 | 125785 | 61 | 32023 | 127 | 94830 |
| Not allowed by investigator country regulations | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1534 |
| Other | 4 | 2572 | 3 | 2214 | 1 | 358 | 2 | 634 |
| Total | 303 | 245258 | 200 | 193765 | 103 | 51493 | 198 | 137283 |

Study CT-P10 3.3 and Study CT-P10 3.4

*: Subjects switched to CT-P10 at 13 months after the reference product treatment from Study CT-P10 3.4.

Subject time (days) = ([Date of End of Study Participation], [Date of End of Study], [Date of First Exposure of Switch - 1] or [Date of Death], whichever is earlier) - [Date of First Exposure to Treatment] + 1 or ([Date of End of Study] or [Date of Death], whichever is earlier) –[Date of First Exposure of Switch] + 1

**INDICATION: Rheumatoid Arthritis (All Trial Population)**

| | CT-P10 1000mg | | | | | | Rituximab Reference Product 1000mg | |
|---|---|---|---|---|---|---|---|---|
| | Total | | CT-P10 only | | Switched from Rituximab Reference Product 1000mg* | | | |
| **Ethnic Origin** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| White | 241 | 89643 | 160 | 75062 | 81 | 14581 | 173 | 69296 |
| Black | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asian | 35 | 13310 | 27 | 11805 | 8 | 1505 | 21 | 7338 |
| Other | 116 | 44379 | 76 | 37126 | 40 | 7253 | 68 | 28534 |
| Unspecified | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 392 | 147332 | 263 | 123993 | 129 | 23339 | 262 | 105168 |

Study CT-P10 1.1, Study CT-P10 1.3 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 80 weeks after the reference product treatment.

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) - Date of First Exposure to Treatment + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

## Table 6 Part II.SIII.5: Special Population

| INDICATION: Rheumatoid Arthritis (Randomised, Blinded Trial Population) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CT-P10 1000mg | | | | | | Rituximab Reference Product 1000mg | |
| | Total | | CT-P10 only | | Switched from Rituximab Reference Product 1000mg* | | | |
| **Special Population** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| Children [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pregnant women [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lactating women [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal impairment [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hepatic impairment [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac impairment [2] | 2 | 689 | 2 | 689 | 0 | 0 | 1 | 482 |
| Patients with prior history of hepatitis B virus infection [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| FcγR IIIa sub-population; F/F | 154 | 55841 | 110 | 48238 | 44 | 7603 | 96 | 38303 |
| FcγR IIIa sub-population; F/V+V/V | 150 | 52595 | 100 | 43983 | 50 | 8612 | 128 | 51219 |
| Total[#] | 304 | 108436 | 210 | 92221 | 94 | 16215 | 224 | 89522 |

Study CT-P10 1.1 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 52 weeks after the reference product treatment.

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) - Date of First Exposure to Treatment + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

[1] Patients who meet this definition were ineligible for all studies according to the Inclusion/ Exclusion criteria.

[2] Patients defined as those patients who satisfy at least one of the following criteria:
1. Patients whose screening ECG test was reported as abnormal and clinically significant.
2. Patients who had a medical history of cardiac failure, chronic cardiac failure, or congestive cardiac failure

[#] Total number of patients who corresponds to any of the special population terms above. Patients are only counted once.

| INDICATION: Non-Hodgkin's Lymphoma (Randomised, Blinded Trial Population) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CT-P10 375mg/m² | | | | | | Rituximab Reference Product 375mg/m² | |
| | Total | | CT-P10 only | | Switched from Rituximab Reference Product* | | | |
| **Special Population** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** | **Subjects (n)** | **Subject-time (days)** |
| Children [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pregnant women [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lactating women [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal impairment [1] | 1 | 456 | 0 | 0 | 1 | 456 | 1 | 420 |
| Hepatic impairment [1] | 1 | 456 | 0 | 0 | 1 | 456 | 1 | 420 |
| Cardiac impairment [2] | 4 | 2684 | 2 | 1882 | 2 | 802 | 3 | 2213 |
| Patients with prior history of hepatitis B virus infection [1] | 13 | 8633 | 6 | 5210 | 7 | 3423 | 10 | 5003 |
| FcγR IIIa sub-population; F/F | 103 | 81530 | 63 | 62143 | 40 | 19387 | 76 | 51590 |
| FcγR IIIa sub-population; F/V+V/V | 131 | 110952 | 88 | 87547 | 43 | 23405 | 72 | 49834 |
| Total[#] | 234 | 192482 | 151 | 149690 | 83 | 42792 | 150 | 103589 |

Study CT-P10 3.3 and Study CT-P10 3.4

*: Subjects switched to CT-P10 at 13 months after the reference product treatment from Study CT-P10 3.4.

Subject time (days) = ([Date of End of Study Participation], [Date of End of Study], [Date of First Exposure of Switch - 1] or [Date of Death], whichever is earlier) – [Date of First Exposure to Treatment] + 1
or ([Date of End of Study] or [Date of Death], whichever is earlier) –[Date of First Exposure of Switch] + 1

[1] Patients who meet this definition were ineligible for all studies according to the Inclusion/ Exclusion criteria.

[2] Patients defined as those patients who satisfy at least one of the following criteria:
1. Patients whose screening ECG test was reported as abnormal and clinically significant.
2. Patients who had a medical history of cardiac failure, chronic cardiac failure, or congestive cardiac failure.

[#] Total number of patients who corresponds to any of the special population terms above. Patients are only counted once.

| INDICATION: Rheumatoid Arthritis (All Trial Population) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CT-P10 1000mg | | | | | | Rituximab Reference Product 1000mg | |
| | Total | | CT-P10 only | | Switched from Rituximab Reference Product 1000mg* | | | |
| Special Population | Subjects (n) | Subject-time (days) | Subjects (n) | Subject-time (days) | Subjects (n) | Subject-time (days) | Subjects (n) | Subject-time (days) |
| Children [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pregnant women [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lactating women [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal impairment [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hepatic impairment [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac impairment [2] | 3 | 870 | 2 | 689 | 1 | 181 | 1 | 482 |
| Patients with prior history of hepatitis B virus infection [1] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| FcγR IIIa sub-population; F/F | 160 | 60765 | 110 | 51883 | 50 | 8882 | 96 | 38303 |
| FcγR IIIa sub-population; F/V+V/V | 162 | 58215 | 100 | 46916 | 62 | 11299 | 128 | 51219 |
| Total[#] | 322 | 118980 | 210 | 98799 | 112 | 20181 | 224 | 89522 |

Study CT-P10 1.1, Study CT-P10 1.3 and Study CT-P10 3.2

*: Subjects switched to CT-P10 between 48 and 80 weeks after the reference product treatment.

Subject time (days) = (([Date of Last Visit] or [Date of First Exposure of Switch - 1]) - Date of First Exposure to Treatment + 1)
or ([Date of Last Visit] –[Date of First Exposure of Switch]+1)

[1] Patients who meet this definition were ineligible for all studies according to the Inclusion/ Exclusion criteria.

[2] Patients defined as those patients who satisfy at least one of the following criteria:
1. Patients whose screening ECG test was reported as abnormal and clinically significant.
2. Patients who had a medical history of cardiac failure, chronic cardiac failure, or congestive cardiac failure.

[#] Total number of patients who corresponds to any of the special population terms above. Patients are only counted once.

# PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

**Patients who have a known hypersensitivity to rituximab, excipients, or murine proteins.**

Reason for exclusion: Patients who have an experience hypersensitivity reaction to rituximab, murine proteins, or to any of the excipients were excluded from the pivotal clinical studies to preventing safety issues. Patients with a known hypersensitivity would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.

It is contraindicated to patients with a known hypersensitivity to rituximab, murine proteins, or to any of the excipients, and it is not recommended that these patients group will be treated with Truxima/Blitzima in line with the reference product MabThera (MabThera SmPC).

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to known hypersensitivity to the products is not included as missing information aligned to the reference product MabThera RMP.

**Patients who have active, severe infections.**

Reason for exclusion: Patients who have active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections) were excluded from the pivotal clinical studies to preventing safety issue. Infections are a frequent complication of treatment and major cause of morbidity and mortality in patients especially with haematological malignancies.

It is contraindicated to patients with active, severe infections, and it is not recommended that these patients group will be treated with Truxima/Blitzima in line with the reference product MabThera (MabThera SmPC)

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to active, severe infections is not included as missing information aligned to the reference product MabThera RMP. Infections including serious infections during/after rituximab treatment has been included in this RMP as an important identified risk.

**Patients who is in a severely immunocompromised state.**

Reason for exclusion: Patients who are in a severely immunocompromised state (e.g., where levels of CD4 or CD8 are very low) were excluded from the pivotal clinical studies to preventing safety issue. Physicians should exercise caution when considering the use of rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, e.g., hypogammaglobulinaemia.

It is contraindicated to patients in a severely immunocompromised state, and it is not recommended that these patients group will be treated with Truxima/Blitzima in line with the reference product MabThera (MabThera SmPC)

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to a severely immunocompromised state is not included as missing information aligned to the reference product MabThera RMP.

**Patients who have a severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease (applies to autoimmune indications only).**

Reason for exclusion: Patients who have a severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease were excluded from the pivotal clinical studies for autoimmune diseases to preventing safety issue. Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with rituximab.

It is contraindicated to patients who have a severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease, and it is not recommended that these patients group will be treated with Truxima/Blitzima in line with the reference product MabThera (MabThera SmPC)

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to a severe heart failure or severe, uncontrolled cardiac disease is not included as missing information aligned to the reference product MabThera RMP.

**Patients who have taken more than two biologics agents (applies to rheumatoid arthritis indication only).**

Reason for exclusion: Patients who have taken more than two biologics agents were excluded from the pivotal clinical studies for rheumatoid arthritis to preventing confounding interpretation of efficacy endpoints. Sequential treatment with other biological therapies may increase the risk of clinically relevant infection.

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to taking more than two biologics agents is not included as missing information aligned to the reference product.

**Patients who have taken live or live-attenuated vaccine within 8 weeks prior to randomisation, and killed vaccines within 4 weeks prior to treatment with rituximab.**

Reason for exclusion: Patients who have taken live or live-attenuated vaccine within 8 weeks prior to randomisation, and killed vaccines within 4 weeks prior to treatment with rituximab were excluded from the pivotal clinical studies because the safety of immunisation with live viral vaccines following rituximab (reference product) therapy has not been studied. Response rates to non-live vaccines may be reduced.

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to vaccination following rituximab therapy is not included as missing information aligned to the reference product MabThera RMP.

**Patients who have B-lymphocyte (B-cell) depletion or history of treatment with B-cell–targeted biologic agent (applies to rheumatoid arthritis indication only).**

Reason for exclusion: Patients who have B-lymphocyte (B-cell) depletion or history of treatment with B-cell–targeted biologic agent were excluded from the pivotal clinical studies to reduce the likelihood of adverse reactions (e.g. severe infection) due to pharmacodynamic interaction with rituximab leading to profound B-cell depletion, and to preventing confounding interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to B-lymphocyte (B-cell) depletion or history of treatment with B-cell–targeted biologic agent is not included as missing information aligned to the reference product MabThera RMP.

**Patients who have history of any malignancy within the previous 5 years except completely excised or cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.**

Reason for exclusion: Patients who have history of any malignancy within the previous 5 years except completely excised or cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma were excluded from the pivotal clinical studies to reduce the risk of premature withdrawal from the study for reasons not related to study medication. Immunomodulatory drugs may increase the risk of malignancy.

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to malignancy is not included as missing information aligned to the reference product MabThera RMP.

**Patients who have history of lymphoma, lymphoproliferative disease, or bone marrow hypoplasia (applies to rheumatoid arthritis indication only).**

Reason for exclusion: Patients who have history of lymphoma, lymphoproliferative disease, or bone marrow hypoplasia were excluded from the pivotal clinical studies to reduce the risk of premature withdrawal from the study for reasons not related to study medication. Immunomodulatory drugs may increase the risk of malignancy.

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to malignancy is not included as missing information aligned to the reference product MabThera RMP.

**Patients who have history of organ transplantation, including corneal graft/transplantation (applies to rheumatoid arthritis indication only).**

Reason for exclusion: Patients who have history of organ transplantation, including corneal graft/transplantation were excluded from the pivotal clinical studies to reduce the risk of premature withdrawal from the study for reasons not related to study medication. Rituximab has immunosuppressant properties which may affect the management of the patient with a transplant.

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The risk related to organ transplantation, including corneal graft/transplantation is not included as missing information aligned to the reference product MabThera RMP.

**Female patients who are currently pregnant or breastfeeding or are planning to become pregnant or breastfeed within 12 months of the last dose of rituximab.**

Reason for exclusion: Female patients who are currently pregnant or breastfeeding or is planning to become pregnant or breastfeed within 12 months of the last dose of rituximab were excluded from the pivotal clinical studies to reduce the risk of premature withdrawal from the study for reasons not related to study medication. Rituximab is not recommended during pregnancy or when nursing an infant.

Is it considered to be included as missing information?: No

Rationale: Truxima/Blitzima is a biosimilar medicinal product to the reference product MabThera. The safety concern ‘Use during in pregnancy and lactation (all indications)’ is no longer presented as missing information aligned to the reference product MabThera RMP.

## SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure or cumulative exposure.

Adverse drug reactions (ADRs) with a frequency greater than approximately 1 in 130 subjects with rheumatoid arthritis and 1 in 101 subjects with Non-hodgkin’s lymphoma may be detected with a data set of this size.

ADRs which require an exposure of longer than 30 months to develop in subjects with rheumatoid disease, or 54 months in subjects with lymphoma would not be expected to be detected in the safety data set.

## SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

**Table 7 Part II.SIV.2: Exposure of special populations included or not in clinical trial development programmes**

| Type of special population | Exposure |
|---|---|
| **Pregnant or breastfeeding women**<br><br>There have been no pregnancies reported in patients treated with CT-P10 up to the data-lock point of clinical data for this RMP (18 October 2019).<br><br>Pregnancy outcomes following exposure to the reference product have been reported in the literature (Chakravarty *et al.* 2011). Up to 30 November 2009, 231 pregnancies associated with maternal rituximab exposure were identified in the rituximab global drug safety database. Maternal indications included lymphoma, autoimmune cytopenias, and other autoimmune diseases. Most cases were confounded by concomitant use of potentially teratogenic medications and severe underlying disease. Of 153 pregnancies with known outcomes, 90 resulted in live births. Twenty-two infants were born prematurely with one neonatal death at 6 weeks. Eleven neonates had haematological abnormalities; none had corresponding infections. Four neonatal/ perinatal infections were reported (fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis). Two congenital malformations were reported - clubfoot in one twin, and cardiac malformation in a singleton birth. One maternal death from pre-existing autoimmune thrombocytopenia occurred.<br><br>The risk following exposure of the unborn child that may be attributable to rituximab, to the exclusion of all other medicines received by the patient, cannot be estimated from the available data. B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to the reference product during pregnancy (Chakravarty *et al.* 2011). Similar effects have | Not included in the clinical development program |

| | |
|---|---|
| been observed in animal studies (MabThera SmPC).<br><br>Rituximab is not recommended to be administered during pregnancy. Women should be advised to avoid pregnancy during rituximab exposure and for 12 months after the last treatment has been administered. | |
| **Patients with relevant comorbidities:**<br>• Patients with hepatic impairment<br><br>Rituximab is an immunoglobulin. It is not biotransformed in the liver, and does not undergo hepatic excretion. There is no evidence of hepatotoxicity in clinical use for the reference product (MabThera SmPC; van Vollenhoven *et al.* 2010).<br>• Patients with renal impairment<br><br>Rituximab does not undergo renal excretion. There is no evidence of nephrotoxicity in clinical use for the reference product (MabThera SmPC; van Vollenhoven *et al.* 2010).<br>• Patients with cardiovascular impairment<br><br>Rituximab is contraindicated in patients with rheumatoid arthritis, GPA, MPA or PV who have severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease. Such patients were excluded from clinical trials with CT-P10.<br>• Immunocompromised patients<br><br>• Patients with a disease severity different from inclusion criteria in clinical trials<br><br>CT-P10 has been studied in two controlled clinical trials and one maintenance study in subjects with rheumatoid arthritis.<br><br>Rituximab is indicated in combination with methotrexate for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease- | <br><br>One subject with hepatic impairment was treated with CT-P10 for Non-Hodgkin's lymphoma in clinical studies (Table 6).<br><br><br><br>One subject with renal impairment was treated with CT-P10 for Non-Hodgkin's lymphoma in clinical studies (Table 6).<br><br><br><br>There are two and four subjects with cardiac impairment (defined as an abnormal electrocardiogram, or a history of cardiac failure) who were treated with CT-P10 for rheumatoid arthritis and Non-Hodgkin's lymphoma in clinical studies, respectively (Table 6).<br><br>Not included in the clinical development program<br><br>Not included in the clinical development program |

| | |
|---|---|
| modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies. The subjects included in clinical trials with CT-P10 were required to have severe rheumatoid arthritis, or rheumatoid arthritis which was refractory to other treatments (consistent with the indication authorised for the reference product). Subjects with less severe rheumatoid disease have not been studied and would not generally be expected to receive rituximab.<br><br>CT-P10 has been studied in one controlled clinical trial in advanced follicular lymphoma (subjects with stage III-IV follicular lymphoma treated in combination with cyclophosphamide, vincristine, and prednisone). Rituximab is indicated for: the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy; maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy; for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy; and 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. It is plausible therefore, that CT-P10 may be used to treat patients with less severe non-Hodgkin's lymphoma than those studied in Study CT-P10 3.3. The therapeutic effects of CT-P10 have been shown to be clinically indistinguishable from those of the reference product in clinical studies conducted to date. CT-P10 is therefore, likely to be as effective for the treatment of non-Hodgkin's lymphoma with a disease severity that differs from the inclusion criteria in Study CT-P10 3.3 as the reference product. The efficacy and safety of CT-P10 are compared to those of the reference product in a completed controlled | |

| | |
|---|---|
| study in patients with Grade 1 to 3a (Ann Arbor stage II-IV) low-tumour burden follicular lymphoma (CT-P10 3.4). | |
| **Population with relevant different ethnic origin** | The majority of subjects in the rheumatoid arthritis data set exposed to CT-P10 in Study CT-P10 1.1, Study CT-P10 1.3 and Study CT-P10 3.2, were White (n=241). Thirty-five subjects were Asian. No black subjects with rheumatoid arthritis have been exposed to CT-P10 (Table 5).<br>The majority of subjects in the Non-Hodgkin's lymphoma data set exposed to CT-P10 in Study CT-P10 3.3 and Study CT-P10 3.4, were White (189 subjects) or Asian (96 subjects). There were no subjects of Native Hawaiian or other pacific islander (Table 5). |
| **Subpopulations carrying relevant genetic polymorphisms**<br>FcγRIIIa polymorphisms have been reported to correlate with response to rituximab in patients with non-Hodgkin's lymphoma (NHL) (Cartron *et al.,* 2002; Weng & Levy 2009) where the high-affinity FcγRIIIa V/V 158 allotype correlates with significantly better responses (90% vs. 67%) at one year (Cartron *et al.,* 2002). In RA studies the relationship between high affinity V/V158 or V/F159 FcγRIII allotypes and clinical outcomes with rituximab has also been suggested in some studies but not in others (Kastbom *et al*. 2012; Sarsour *et al*. 2013; Quartuccio *et al*. 2014; Robledo *et al*. 2012; Ruyssen-Witrand *et al*. 2012). | FcγRIIIa receptor subtyping was performed on 322 subjects in the rheumatoid arthritis data set exposed to CT-P10 in Study CT-P10 1.1, Study CT-P10 1.3 and Study CT-P10 3.2. Similar numbers of subjects with the FcγRIIIa F/F variant (n=160) and the FcγRIIIa F/V+V/V variant (n=162) were treated with CT-P10 (Table 6).<br>FcγRIIIa receptor subtyping was obtained on 234 subjects in the Non-Hodgkin's lymphoma data set exposed to CT-P10 in Study CT-P10 3.3 and Study CT-P10 3.4. 103 subjects with the FcγRIIIa F/F variant and 131 subjects with the FcγRIIIa F/V+V/V variant were treated with CT-P10 (Table 6). |
| **Other**<br>**Children**<br>No clinical studies have been conducted with CT-P10 in the paediatric patient population. The reference product is not authorised for use in children.<br>According to Regulation (EC) No 1901/2006 the requirement to submit a paediatric | Not included in the clinical development program |

| | |
|---|---|
| investigation plan does not apply to similar biological medicinal products. No paediatric investigation plan has been submitted for CT-P10.<br><br>Administration of rituximab to children is unauthorised (off-label) use. | |
| **Elderly**<br><br>The use of CT-P10 has currently been documented in studies involving subjects with rheumatoid arthritis and advanced follicular lymphoma. | Ninety-one subjects over the age of 60 years with rheumatoid arthritis have been treated with CT-P10 in clinical studies (Table 3). 132 subjects over the age of 60 years with Non-Hodgkin's lymphoma have been treated with CT-P10 in clinical study (Table 3). |
| **Infusion-related reactions (IRRs)**<br><br>Infusion-related reactions (IRRs), which may be severe, occur very commonly during administration of rituximab. | In subjects treated with CT-P10 for rheumatoid arthritis in all clinical studies, the crude incidence of IRRs was 19.4%. In subjects treated with CT-P10 for Non-Hodgkin's lymphoma data set exposed to CT-P10 in Study CT-P10 3.3 and Study CT-P10 3.4, the crude incidence of IRRs were 45.7% and 19.7% to respective studies. IRRs may be associated with reactions such as hypertension, hypotension, cardiac dysrhythmia, or tachycardia that would be expected to worsen haemodynamic disturbances in patients with pre-existing cardiac impairment. |
| **Anti-drug antibodies (ADA)** | Anti-drug antibodies were measured throughout the observation periods in the rheumatoid arthritis data set exposed to CT-P10 in Study CT-P10 1.1 and the maintenance Study CT-P10 1.3.<br><br>The majority of subjects had negative ADA test results at each time-point in these studies. In general, the proportion of patients with positive ADA was similar in the CT-P10 and MabThera® treatment groups during the study. In the rheumatoid arthritis study CT-P10 1.1, the number of subjects who had positive ADA at Week 24 of the core and extension study periods was 18 (17.6%) and 12 (20.0%) subjects in the CT-P10 treatment group and 9 |

| | |
|---|---|
| | (17.6%) and 5 (21.7%) subjects in the MabThera® treatment group, respectively.<br><br>In the rheumatoid arthritis study CT-P10 3.2, the majority of subjects also had negative ADA test results at each time-point. At baseline, the number of subjects who had positive ADA was 19 (11.8%) in the CT-P10 treatment group and 20 (9.5%) in the group treated with the reference products (MabThera® + Rituxan®). However, at Week 48 of the main study period, for the patients who received both first and second courses of treatment, the proportion was lower in the CT-P10 group compared with the reference product treatment group (4.9% cf. 9.2%). In addition, at Week 24 of the extension study period, the proportion of the patients who had positive ADA was 4.1%, 3.1%, and 10.1% in the group of CT-P10 maintenance, the reference product maintenance, and switched from the reference product, respectively.<br><br>In the advanced follicular lymphoma study (CT-P10 3.3), the majority of subjects also had negative ADA test results at each time-point. At baseline, the number of subjects who had positive ADA was 5 (7.1%) in the CT-P10 group and 8 (11.4%) in the group treated with the reference rituximab product (Rituxan®). Among 7 subjects (3 (4.3%) subjects in the CT-P10 group and 4 (5.7%) subjects in the reference product treatment group) who had at least 1 posttreatment positive result for ADA test during the overall study period, the number of subjects who had at least 1 posttreatment positive result for ADA test in the CT-P10 group during the Core Study Period was 3 (4.3%) compared with 2 (2.9%) in the reference product treatment group. During the Maintenance Study Period, 1 (1.4%) subject had at least 1 posttreatment positive result for ADA test in the CT-P10 group while 2 (2.9%) subjects had in reference product treatment group. The results suggest a similar propensity for anti-drug antibody formation in both treatment groups. |

| | |
|---|---|
| | In the low tumour burden follicular lymphoma study (CT-P10 3.4), the majority of subjects had negative ADA test results. The proportion of patients with positive ADA results at posttreatment was similar in the 2 treatment groups. A total of 4 patients (1 (0.8%) for CT-P10 and 3 (2.3%) for the reference product, Rituxan®) had at least 1 positive-ADA result at posttreatment visits. There was no ADA development after switch from the reference product, Rituxan® to CT-P10. |

# PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

## SV.1 Post-authorisation exposure

### SV.1.1 Method used to calculate exposure

The estimate of the cumulative patient exposure since launch was generally calculated based on the sales volumes of active ingredient in milligram and the defined daily dose (DDD) provided by the WHO Collaborating Centre for Drug Statistic Methodology in Oslo.

The formula used by Celltrion for estimating the patient exposure is as described below:

$$\textit{Patient Exposure (patient dose)} = \frac{\textit{Quantity of rituximab sold (g)}}{\textit{DDD (g/patient)}}$$

Therefore, the patient exposure from marketing experience can be presented in patient-doses but not as patient-years. However, no DDD has been established for rituximab since the dosing and schedule vary based on indications and dosing is intermittent not daily. Therefore, assuming DDD is 1 g per patient, which is the maximal dose recommended based on mg/m$^2$ dosing, the patient exposure to rituximab has been calculated in patient doses using the above formula.

### SV.1.2 Exposure

Total Celltrion patient exposure is calculated to be 2,311,830 patient-doses (based on the total sales amount available by 30 September 2023; 2,311.8 kg).

**Table 8 SV.1: Post-authorisation exposure – cumulative exposure from first launch date**

| Region | Total number of 500 mg vial sold* | Total number of 100 mg vial sold* | Total amount sold in mg | Total Patient-dose |
|---|---|---|---|---|
| **European Union** | 1,847,747 | 755,943 | 999,467,800 | 999,468 |
| **North America** | 1,008,347 | 1,312,715 | 635,445,000 | 635,446 |
| **Rest of the World** | 1,184,451 | 846,914 | 676,916,900 | 676,916 |
| **Total** | **4,040,545** | **2,915,572** | **2,311,829,700** | **2,311,830** |

Cumulative exposure is based on sales data from the initial launch date to 30 September 2023.
* The number represents the total number of vials shipped out from storage.
**Note**: Rounding errors may be introduced in the total figure.

# PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

## Potential for misuse for illegal purposes

Abuse is unlikely. Truxima/Blitzima will only be administered by intravenous infusion by healthcare professionals. Rituximab has no psychoactive effects, and no other properties that might appeal to people intent upon misusing it for illegal purposes.

# PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

## SVII.1 Identification of safety concerns in the initial RMP submission

Since this is not initial RMP submission, this section is not applicable.

### SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

**Reason for not including an identified or potential risk in the list of safety concerns in the RMP:**

Not applicable.

### SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

## SVII.2 New safety concerns and reclassification with a submission of an updated RMP

To be harmonised with the list of safety concerns of the reference product, MabThera according to the most up-to-date MabThera RMP version 25.1, the important identified risks 'Hepatitis B virus (HBV) reactivation' and 'Hypogammaglobulinaemia', important potential risks 'Malignancy', 'Impact on cardiovascular disease', 'Relapse of GPA/MPA', and 'Administration route error', and missing information 'Use during pregnancy or lactation' and 'Long-term use in GPA/MPA patients' of Truxima/Blitzima have been removed from the list of safety concerns.

## SVII.3 Details of important identified risks, important potential risks, and missing information

The data available for the assessment of the risk of Truxima/Blitzima are derived from post-marketing experiences and completed trials in RA (Study CT-P10 1.1, Study CT-P10 1.3, and Study CT-P10 3.2) and in NHL (Study CT-P10 3.3 and Study CT-P10 3.4).

The description that follows provides details on the identified and potential risks that have been described for the intravenous formulation of the reference product, based on the clinical trial data and post-marketing experiences data currently available for Truxima/Blitzima.

### SVII.3.1. Presentation of important identified risks and important potential risks

**Important Identified Risk- Infections including serious infections (all indications)**

**Potential mechanisms:**

Immunosuppression

**Evidence source(s) and strength of evidence:**

It is not possible to make meaningful generalisations about the background incidence and prevalence of infections as these vary with time, location, the nature of the infection, and the susceptibility of the population exposed to risk, even within the EU.

Truxima/Blitzima is a biosimilar medicinal product to the reference product of MabThera. The evidence of the above mentioned risk is derived from the MabThera RMP, hence the strength of the evidence is consistent with that included in the MabThera RMP.

**Characterisation of the risk:**

Clinical studies

Frequency:

| **Indication – rheumatoid arthritis** | | | | |
|---|---|---|---|---|
| **Studies included:** CT-P10 1.1, CT-P10 1.3, CT-P10 3.2 | | | | |
| **Treatment** | **CT-P10** | | | **Rituximab reference product** |
| | **Total** | **CT-P10 only** | **Switched from rituximab reference product** | |
| N | 392 | 263 | 129 | 262 |
| No. of Subjects with TEAEs [1] n (%) | 123 ( 31.4%) | 104 ( 39.5%) | 19 ( 14.7%) | 95 ( 36.3%) |
| Total No. of TEAEs | 234 | 206 | 28 | 164 |
| Subjects with TEAEs/100 PY | 30.493 | 30.636 | 29.735 | 32.994 |
| 95% CI for 100 PY | (25.343, 36.382) | (25.032, 37.120) | (17.902, 46.434) | (26.694, 40.333) |

[1] Includes all subjects who had one or more occurrences of a treatment emergent adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

Note. 1 year = 365.25 days

MedDRA dictionary, version 18.1

| **Indication – Non-Hodgkin's lymphoma** | | | | |
|---|---|---|---|---|
| **Studies included:** CT-P10 3.3, CT-P10 3.4 | | | | |
| **Treatment** | **CT-P10** | | | **Rituximab reference product** |
| | **Total** | **CT-P10 only** | **Switched from rituximab reference product** | |
| N | 303 | 200 | 103 | 198 |
| No. of Subjects with TEAEs [1] n (%) | 125 ( 41.3%) | 94 ( 47.0%) | 31 ( 30.1%) | 73 ( 36.9%) |
| Total No. of TEAEs | 219 | 177 | 42 | 152 |
| Subjects with TEAEs/100 PY | 18.616 | 17.719 | 21.989 | 19.422 |
| 95% CI for 100 PY | (15.495, 22.180) | (14.319, 21.684) | (14.940, 31.212) | (15.224, 24.420) |

[1] Includes all subjects who had one or more occurrences of a treatment emergent adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

Note. 1 year = 365.25 days

MedDRA dictionary, version 18.1

Seriousness/outcomes:

| **Indication – rheumatoid arthritis** | | | | |
|---|---|---|---|---|
| **Studies included:** CT-P10 1.1, CT-P10 1.3, CT-P10 3.2 | | | | |
| **Treatment** | **CT-P10** | | | **Rituximab reference product** |
| | **Total** | **CT-P10 only** | **Switched from rituximab reference product** | |
| N | 392 | 263 | 129 | 262 |
| All adverse events N (%) [1] | 123 ( 31.4%) | 104 ( 39.5%) | 19 ( 14.7%) | 95 ( 36.3%) |
| | | | | |
| Serious | 4 ( 1.0%) | 3 ( 1.1%) | 1 ( 0.8%) | 5 ( 1.9%) |
| | | | | |
| Outcomes [2] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| Recovered | 114 ( 29.1%) | 97 ( 36.9%) | 17 ( 13.2%) | 95 ( 36.3%) |
| Recovering | 4 ( 1.0%) | 3 ( 1.1%) | 1 ( 0.8%) | 0 |
| Did not recover | 4 ( 1.0%) | 3 ( 1.1%) | 1 ( 0.8%) | 0 |
| Fatal | 1 ( 0.3%) | 1 ( 0.4%) | 0 | 0 |

[1] Includes all subjects who had one or more occurrences of a treatment emergent adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe outcome is counted - Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing

| **Indication – Non-Hodgkin's lymphoma** | | | | |
|---|---|---|---|---|
| **Studies included:** CT-P10 3.3, CT-P10 3.4 | | | | |
| **Treatment** | **CT-P10** | | | **Rituximab reference product** |
| | **Total** | **CT-P10 only** | **Switched from rituximab reference product** | |
| N | 303 | 200 | 103 | 198 |
| All adverse events N (%) [1] | 125 ( 41,3%) | 94 ( 47.0%) | 31 ( 30.1%) | 73 ( 36.9%) |
| | | | | |
| Serious | 9 ( 3.0%) | 8 ( 4.0%) | 1 ( 1.0%) | 7 ( 3.5%) |
| | | | | |
| Outcomes [2] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| Recovered | 121 ( 39.9%) | 90 ( 45.0%) | 31 ( 30.1%) | 68 ( 34.3%) |
| Recovering | 0 | 0 | 0 | 1 ( 0.5%) |
| Did not recover | 4 ( 1.3%) | 4 ( 2.0%) | 0 | 3 ( 1.5%) |
| Fatal | 0 | 0 | 0 | 1 ( 0.5%) |

[1] Includes all subjects who had one or more occurrences of a treatment emergent adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe outcome is counted - Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing

Two serious infections were reported in Study CT-P10 1.1; one case of diverticulitis in a subject treated with CT-P10 and one case of lobar pneumonia in a patient treated with the reference product.

Seven serious infections were reported in Study CT-P10 3.2; one case of cellulitis due to thrombosis of the right brachial vein, and one case of pneumonia in subjects treated with CT-P10, and one case each of bronchitis, cellulitis, eczema infected, and pneumocystis jirovecii pneumonia in subjects treated with the reference product.

The case of cellulitis due to thrombosis of the right brachial vein in a subject treated with CT-P10 had a fatal outcome. It refers to a 58-year-old woman treated with CT-P10 for approximately two months who developed thrombosis of the right brachial vein due to reactive thrombocytosis which was related to her rheumatoid disease and not to treatment with CT-P10. Treatment was discontinued due to cellulitis, which was also assessed as unrelated to treatment with CT-P10. She died due to acute respiratory distress syndrome one month after cellulitis started.

The case of pneumonia in the subject treated with CT-P10 was reported during the extension study period and the subject was switched from the reference product treatment group.

Overall, 16 serious infections were reported in 12 patients from Study CT-P10 3.3; 4 cases of pneumonia, 1 case of lower respiratory tract infection, campylobacter gastroenteritis, abdominal infection, herpes zoster, appendicitis, and sialoadenitis each in 8 subjects treated with CT-P10. There were 1 case of encephalitis, bronchitis, pneumonia, upper respiratory tract infection, respiratory tract infection, and sinobronchitis each in 4 subjects treated with the reference product. All of patients who experienced serious infections recovered from the events.

One serious case of pneumonia has been reported with a severity of grade 4 in a 63-year-old woman treated with CT-P10. The subject experienced pneumonia 12 days after the administration of the rituximab treatment, and the event was resolved. The event was considered definitely related to CT-P10, but also possibly related to other treatment; cyclophosphamide, vincristine, and prednisolone.

One serious case of infection was reported in a subject exposed to CT-P10 after switching from Study CT-P10 3.4; a 57-year-old male who was treated with CT-P10 switched from the reference product experienced a grade 3 urinary tract infection. The patient was recovered from the event and the event was resolved. The event was suggestive to be considered as probably related to CT-P10.

Severity and nature of risk:

| **Indication – rheumatoid arthritis** | | | | |
|---|---|---|---|---|
| **Studies included:** CT-P10 1.1, CT-P10 1.3, CT-P10 3.2 | | | | |
| **Treatment** | **CT-P10** | | | **Rituximab reference product** |
| | **Total** | **CT-P10 only** | **Switched from rituximab reference product** | |
| N | 392 | 263 | 129 | 262 |
| All adverse events N (%) [1] | 123 ( 31.4%) | 104 ( 39.5%) | 19 ( 14.7%) | 95 ( 36.3%) |
| | | | | |
| Severity [2] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| Grade 1 | 18 ( 4.6%) | 17 ( 6.5%) | 1 ( 0.8%) | 19 ( 7.3%) |
| Grade 2 | 100 ( 25.5%) | 83 ( 31.6%) | 17 ( 13.2%) | 72 ( 27.5%) |
| Grade 3 | 3 ( 0.8%) | 2 ( 0.8%) | 1 ( 0.8%) | 4 ( 1.5%) |
| Grade 4 | 1 ( 0.3%) | 1 ( 0.4%) | 0 | 0 |
| Grade 5 | 1 ( 0.3%) | 1 ( 0.4%) | 0 | 0 |

[1] Includes all subjects who had one or more occurrences of a treatment emergent adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe event is counted - Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing

| **Indication – Non-Hodgkin's lymphoma** | | | | |
|---|---|---|---|---|
| **Studies included:** CT-P10 3.3, CT-P10 3.4 | | | | |
| **Treatment** | **CT-P10** | | | **Rituximab reference product** |
| | **Total** | **CT-P10 only** | **Switched from rituximab reference product** | |
| N | 303 | 200 | 103 | 198 |
| All adverse events N (%) [1] | 125 ( 41,3%) | 94 ( 47.0%) | 31 ( 30.1%) | 73 ( 36.9%) |
| | | | | |
| Severity [2] | | | | |
| Missing | 0 | 0 | 0 | 0 |
| Grade 1 | 12 ( 4.0%) | 9 ( 4.5%) | 3 ( 2.9%) | 7 ( 3.5%) |
| Grade 2 | 103 ( 34.0%) | 76 ( 38.0%) | 27 ( 26.2%) | 59 ( 29.8%) |
| Grade 3 | 9 ( 3.0%) | 8 ( 4.0%) | 1 ( 1.0%) | 6 ( 3.0%) |
| Grade 4 | 1 ( 0.3%) | 1 ( 0.5%) | 0 | 0 |
| Grade 5 | 0 | 0 | 0 | 1 ( 0.5%) |

[1] Includes all subjects who had one or more occurrences of a treatment emergent adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe event is counted - Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing

Impact on the quality of life:

It is not possible to predict in individual cases what the impact on the patient may be. The severity of infection and the long-term consequences of infection will vary according to the nature of the infection from mild self-limiting symptoms to an immediately life-threatening condition such as sepsis, which carries a high risk of death and serious potentially irreversible morbidity.

**Risk factors and risk groups:**

- Very young people and elderly people
- Poor nutritional status
- immunosuppressive medications (such as transplant recipients), including steroids
- haematological malignancy
- treatment with chemotherapy drugs or radiation
- splenectomy
- longstanding diabetes, HIV/AIDS, or cirrhosis
- large burns or severe trauma

**Preventability:**

Rituximab should not be given to patients with active potentially serious infection. Patients should receive all appropriate vaccinations before treatment with rituximab. Patients with risk factors should be closely monitored for signs of infection.

**Impact on the risk-benefit balance of the product:**

As biosimilar of MabThera, Truxima/Blitzima was authorised by EMA as verifying comparable safety and efficacy profile to MabThera. The benefit of an effective treatment of NHL, CLL, RA, GPA/MPA, and PV outweighs the important identified risk of infections including serious infections.

**Public health impact:**

Serious infection is the greatest single cause of preventable mortality and morbidity associated with treatment with rituximab.

**Important Identified Risk- Progressive multifocal leukoencephalopathy (PML) (all indications)**

**Potential mechanisms:**

The pathogenesis is not completely understood. Primary infection occurs in childhood in 75% of the population, and the virus remains in a latent form in the kidneys and B-lymphocytes for life. It is hypothesised that clinical disease occurs when the virus in latently infected B-cells becomes activated during periods of severe immunosuppression and subsequently enters the brain, where astrocytes and oligodendrocytes support JC virus replication, causing neurological damage (Garcia-Suarez *et al.* 2005).

The pathophysiology of rituximab-associated PML is unclear, particularly with respect to the role of rituximab. The mechanism underlying viral reactivation after rituximab treatment is probably more complex than simple B-cell depletion. Pre-B-cells that harbour JC virus in a latent state may be released into the circulation to repopulate B-cell functions after differentiation. B-lymphocytes may stimulate cellular immune responses, to both autoantigens and foreign antigens (Carson *et al.* 2009).

**Evidence source(s) and strength of evidence:**

PML is most frequently diagnosed in patients infected with HIV. Incidence rates in HIV-infected patients treated with antiretroviral therapy have been reported to be 0.06% in Switzerland, and 1.3 cases per 1,000 person-years in Denmark (Amend *et al*. 2010).

Incidence rates estimated from a retrospective observational cohort derived from a large US health insurer database have been published for PML in patients without HIV for the period January 2000 to June 2008 (Amend *et al*. 2010). There were 138,469 patients with autoimmune diseases, 25,706 with NHL or CLL, and 8,778 with transplants. Among 699 people who met screening criteria for potential PML, 89 had a diagnosis of PML. Medical records were sought for 24 patients without HIV, and six had confirmed PML upon review of medical records. The PML incidence rate was 2.4 (95% confidence interval [CI] 0.06–13.18) in the systemic lupus erythematosus cohort and 10.8 (95% CI 0.27–60.39) in the autoimmune vasculitis cohort per 100,000 person-years; this rate estimate was based on one case reported in a patient with Wegener's granulomatosis (GPA). In the NHL and CLL cohorts, the incidence rate was 8.3 (95% CI 1.71–24.24) and 11.1 (95% CI 0.28–61.74) per 100,000 person-years. The incidence rate among patients with bone marrow transplantation was 35.4 per 100,000 person-years (95% CI 0.90–197.29). There were no cases of PML among patients with rheumatoid arthritis (95% CI 0.0–2.24), multiple sclerosis (95% CI 0.0–5.24), Sjögren's disease (95% CI 0.0–21.84), or solid organ transplantation (95% CI 0.0–26.81).

In an estimate derived from a hospital discharge sample in the USA (20% of hospitalisations), the cumulative incidence of PML in rheumatoid arthritis was 1 per 100,000 admissions (Molloy ES *et al*. 2008). When patients with defined risk factors for PML were excluded, the incidence of PML in rheumatoid arthritis patients was 0.4 per 100,000 admissions.

There are a number of case reports of PML in the global literature in patients with GPA/MPA. In a review covering the years 1992 to 2010 there were five published reports of PML in patients with GPA, none of whom had been treated with rituximab (Ettinger J *et al.* 1989; Choy DS *et al.* 1992; Morgenstern LB *et al.* 1995; Pagnoux C *et al*. 2003; Wang Y *et al.* 2004). All five patients had received cyclosporin and prednisone.

Studies reporting the incidence of PML among patients with haematological malignancies are limited. Carson *et al.* (2009) referred to a small number of studies assessing the incidence of PML namely,

one population-based study that estimated an incidence of PML of 0.07% based on three cases of PML identified in HIV-negative patients with haematological malignancies over 11 years in Manitoba, Canada (Power *et al.* 2000). A higher incidence of PML of 0.52% was reported in another study in patients with CLL; these patients were treated with fludarabine (Gonzales *et al.* 1999). Carson *et al.* (2009a) concluded that estimating the risk of PML attributable to the underlying malignancy as opposed to immunosuppression due to treatment was complicated by the rarity of the disease and few large trials from which incidences can be determined prospectively. Fludarabine was seen as the drug most closely associated with PML possibly due to the effect of T-cell depletion (Garcia-Suarez *et al.* 2005). Carson *et al.* (2009) also reported that it is not possible accurately to estimate the incidence of PML associated with rituximab among persons with haematological malignancies because of incomplete reporting of PML cases and incomplete data on the number of unique patients with lymphoid malignancies who have received rituximab. It has also been emphasised that the epidemiology of PML in the setting of lymphoid malignancies has changed in recent years; before 1990, most PML cases occurred in Hodgkin's disease. Whereas in recent years, with the development of purine analogues, haematopoietic stem cell transplantation, and rituximab, most PML cases occur in non-HIV-infected persons with NHL or CLL (Garcia-Suarez *et al*. 2005). As rituximab is routinely added to the treatment for haematological malignancies, the contribution of confounding factors to the development of a rare disease such as PML is difficult to estimate.

Bower *et al.*(1997) reviewed B-cell CLL patients seen at the Mayo Clinic from 1987 to 1991 for neurological complications including PML. Among 962 CLL patients there were five cases of PML (0.5%) and three further unconfirmed cases. The incidence rate of confirmed PML was estimated to be 108.5 per 100,000 patient-years (95% CI 35.2-253.1 per 100,000 patient-years). The authors noted that their study may overestimate the incidence of PML in the general CLL population as the Mayo Clinic is a tertiary care centre, and therefore only receives more severe patients.

A single-centre study from Italy reported the incidence of PML amongst 976 subjects with NHL diagnosed between 1994 and 2008 (Tuccori *et al.* 2010). No case of PML was identified amongst 459 subjects that had not been treated with rituximab (Incidence Rate [IR] 0 per 100,000 person-years, 95% CI 0-180). There were five reports of PML among 517 subjects with NHL treated with rituximab (IR 240 0 per 100,000 person-years, 95% CI 100-560). The incidence rates should be interpreted with caution due to possible detection bias due to the use of historical controls, and the effect of publicity concerning the association between PML and rituximab treatment.

Truxima/Blitzima is a biosimilar medicinal product to the reference product of MabThera. The evidence of the above mentioned risk is derived from the MabThera RMP, hence the strength of the evidence is consistent with that included in the MabThera RMP.

**Characterisation of the risk:**

Clinical studies

Frequency:

There are no data. PML has not been observed in clinical studies with Truxima/Blitzima.

PML is very rare in subjects receiving the reference product for the treatment of rheumatoid arthritis (MabThera SmPC). The estimated reporting rate is 3.57 per 100,000 patients (95% CI 1.31-7.77 per 100,000) (MabThera RMP v19.1).

There has been one case of PML reported in a patient treated with the reference product for GPA/MPA (MabThera RMP v19.1).

PML is reported to be a very rare ADR in subjects treated for oncology indications with the reference product (<1/10,000 patients) (MabThera SmPC). Three cases of PML have been reported to have occurred in clinical studies with the reference product for oncology indications (MabThera RMP v19.1).

Seriousness/outcomes:

There are no data. PML has not been observed in clinical studies with Truxima/Blitzima.

The majority of cases of PML that have been reported to have occurred with the reference product have had a fatal outcome (MabThera RMP v19.1).

Severity and nature of risk:

There are no data. PML has not been observed in clinical studies with Truxima/Blitzima.

Impact on the quality of life:

The case fatality rate for patients treated with rituximab has been reported to be 90% (Carson *et al.* 2009). Long-term neurological consequences due to demyelination may occur in survivors.

**Risk factors and risk groups:**

- HIV/AIDS (especially with CD4+ lymphocyte counts less than 200 cells/µL)
- immunosuppressive medications (such as haematopoietic/solid organ transplant recipients), including steroids
- haematological malignancies
- treatment with chemotherapy drugs (especially fludarabine)
- treatment with natalizumab or efalizumab
- autoimmune disorders
- tuberculosis

**Preventability**:

There are no known effective preventive measures. Treatment with rituximab should be stopped immediately if PML is suspected.

**Impact on the risk-benefit balance of the product:**

As biosimilar of MabThera, Truxima/Blitzima was authorised by EMA as verifying comparable safety and efficacy profile to MabThera. The benefit of an effective treatment of NHL, CLL, RA, GPA/MPA, and PV outweighs the important identified risk of PML.

**Public health impact:**

PML is a very rare complication of treatment with rituximab. The public health impact would therefore be expected to be small despite the seriousness of the condition.

## PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Truxima/Blitzima is available only as a concentrate for solution for infusion. The reference product, MabThera is available both as a concentrate for solution for infusion and as a subcutaneous formulation. The safety concerns listed in the following summary are identical to those that have been included in the summary of safety concerns for the reference product based on the pragmatic assumption that the risks for Truxima/Blitzima and the reference product are the same.

**Table 9 Part II.SVIII.1: Summary of safety concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Infections including serious infections (all indications)<br>Progressive multifocal leukoencephalopathy (PML) (all indications) |
| Important potential risks | None |
| Missing information | None |

# PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

## III.1 Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

**Other forms of routine pharmacovigilance activities:**

Not applicable.

## III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities for Truxima/Blitzima.

## III.3 Summary Table of additional Pharmacovigilance activities

**Table 10 Part III.1 On-going and planned additional pharmacovigilance activities**

| Study Status | Summary of objectives | Study concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| Not applicable | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| Not applicable | | | | |
| **Category 3** – Required additional pharmacovigilance activities | | | | |
| Not applicable | | | | |

## PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

# PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

## V.1. Routine Risk Minimisation Measures

This RMP refers to two medicinal products, Truxima and Blitzima, all of which contain the same concentrate for solution for infusion. The risk minimisation measures described in this section refer to the product information for the Truxima, which is identical in all relevant respects to the product information for Blitzima.

**Table 11 Part V.1: Description of routine risk minimisation measures by safety concern**

| Safety concern | Routine risk minimisation activities |
|---|---|
| Identified risk-<br>Infections including serious infections<br>(all indications) | Routine risk communication:<br>SmPC section 4.8: Undesirable effects<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>Recommendation for pneumocystis jirovecii pneumonia (PJP) prophylaxis for patients GPA/MPA in SmPC sections 4.2: Posology and method of administration<br>Precautions to be taken prior to administration for the prevention of serious infection are included in SmPC section 4.3: Contraindications and section 4.4: Special warnings and precautions for use<br>Recommendation for promptly evaluating and treating signs and symptoms of infection following treatment is included in SmPC section 4.4: Special warnings and precautions for use<br>Other routine risk minimisation measures beyond the Product Information:<br>*Legal status*: Restricted medical prescription |
| Identified risk-<br>Progressive multifocal leukoencephalopathy (PML)<br>(all indications) | Routine risk communication:<br>SmPC section 4.4: Special warnings and precautions for use<br>SmPC section 4.8: Undesirable effects<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>Recommendation for monitoring sign and symptom indicative of PML and measures to be taken when sign and symptom suggestive of PML are detected are included in SmPC section 4.4: Special warnings and precautions for use<br>Other routine risk minimisation measures beyond the Product Information: |

| | |
|---|---|
| | *Legal status*: Restricted medical prescription |

## V.2. Additional Risk Minimisation Measures

**Patient alert card (Non-oncology indications)**

Objectives:

To provide patients with a constant reminder that can be carried in a purse or wallet of the important safety concerns associated with rituximab treatment.

To remind the patient to tell his/her doctor of important symptoms that may suggest that he/she has developed infections, especially progressive multifocal leukoencephalopathy.

To provide the patient with a document that he/she can show to any health professional that may not be familiar with the treatment he/she is receiving.

To remind the patient that both he/she and his doctor must keep a record of the brand name and batch number of the rituximab treatment he/she has received.

Patients are to be provided with the patient alert card for the following risks:

- Infections including serious infections
- Progressive multifocal leukoencephalopathy

Rationale for the additional risk minimisation activity:

Infections including PML which can occur during and after the administration of rituximab may be severe, and can be fatal, but preventable cause of serious morbidity and mortality.

All patients who are expected to receive Truxima/Blitzima will be provided with a patient alert card to be aware of the risks associated with this therapy and the need for contacting their doctor immediately if they experience any signs and symptoms of infection especially PML, so that it can be timely diagnosed, followed by appropriate measure considered.

Target audience and planned distribution path:

Patients who receive Truxima/Blitzima must be given a patient alert card that summarises the safety information about the medicine. The patient alert card is provided as part of the product packaging.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be assessed using outcome indicator which is relative reporting rate in relation to drug exposure. The occurrence of infections including PML will be monitored by routine pharmacovigilance activities. The effectiveness of the additional risk minimisation activity will be measured at the data lock point for each scheduled PBRER.

**Rationale for proposing to remove additional risk minimisation measures**

To be harmonised with the reference product, MabThera according to the most up-to-date MabThera RMP version 25.1. The following additional risk minimisation measure will be discontinued: Guide for healthcare professionals and Patient guide for the risk of PML and the risk of infections, including serious infections in non-oncology indications, and Physician information for the risk of administration route error in NHL/CLL indications. Patient alert card will be kept as

additional risk minimisation measure for the risk of PML and the risk of infections, including serious infections in non-oncology indications.

## V.3 Summary of risk minimisation measures

**Table 12 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Identified risk-<br>Infections including serious infections<br>(all indications) | Routine risk minimisation measures:<br>SmPC section 4.2<br>SmPC section 4.3<br>SmPC section 4.4<br>SmPC section 4.8<br>Legal status: Restricted medical prescription<br>Additional risk minimisation measures:<br>Non-oncology indications only<br>– Patient alert card | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |
| Identified risk-<br>Progressive multifocal leukoencephalopathy (PML)<br>(all indications) | Routine risk minimisation measures:<br>SmPC section 4.4<br>SmPC section 4.8<br>Legal status: Restricted medical prescription<br>Additional risk minimisation measures:<br>Non-oncology indications only<br>– Patient alert card | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of risk management plan for Truxima/Blitzima (Rituximab)

This is a summary of the risk management plan (RMP) for Truxima/Blitzima. The RMP details important risks of Truxima/Blitzima, how these risks can be minimised, and how more information will be obtained about Truxima/Blitzima's risks and uncertainties (missing information).

Truxima/Blitzima's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Truxima/Blitzima should be used.

This summary of the RMP for Truxima/Blitzima should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Truxima/Blitzima's RMP.

### I. The medicine and what it is used for

Truxima is authorised for Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukaemia, Rheumatoid Arthritis, Granulomatosis with Polyangiitis and Microscopic Polyangiitis, and Pemphigus Vulgaris; and Blitzima is authorised for Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukaemia, Granulomatosis with Polyangiitis and Microscopic Polyangiitis, and Pemphigus Vulgaris (see SmPCs for the full indication). It contains rituximab as the active substance and it is given by intravenous (IV) infusion.

Further information about the evaluation of Truxima/Blitzima's benefits can be found in Truxima/Blitzima's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

**Truxima**

*https://www.ema.europa.eu/en/medicines/human/EPAR/truxima*

**Blitzima**

*https://www.ema.europa.eu/en/medicines/human/EPAR/blitzima*

### II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Truxima/Blitzima, together with measures to minimise such risks and the proposed studies for learning more about Truxima/Blitzima's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Truxima/Blitzima, these measures are supplemented with *additional risk minimisation measure* mentioned under relevant important risks below.

- Infections including serious infections
- Progressive multifocal leukoencephalopathy

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

### *II.A List of important risks and missing information*

Important risks of Truxima/Blitzima are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Truxima/Blitzima. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | Infections including serious infections (all indications)<br>Progressive multifocal leukoencephalopathy (PML) (all indications) |
| Important potential risks | None |
| Missing information | None |

### *II.B Summary of important risks*

| **Important Identified Risk- Infections including serious infections (all indications)** | |
|---|---|
| Evidence for linking the risk to the medicine | It is not possible to make meaningful generalisations about the background incidence and prevalence of infections as these vary with time, location, the nature of the infection, and the susceptibility of the population exposed to risk, even within the EU. |

| | |
|---|---|
| Risk factors and risk groups | • Very young people and elderly people<br>• Poor nutritional status<br>• immunosuppressive medications (such as transplant recipients), including steroids<br>• haematological malignancy<br>• treatment with chemotherapy drugs or radiation<br>• splenectomy<br>• longstanding diabetes, HIV/AIDS, or cirrhosis<br>• large burns or severe trauma |
| Risk minimisation measures | Routine risk minimisation measures<br>SmPC section 4.2<br>SmPC section 4.3<br>SmPC section 4.4<br>SmPC section 4.8<br>Legal status: Restricted medical prescription<br>Additional risk minimisation measures:<br>Non-oncology indications only<br>– Patient alert card |
| Additional pharmacovigilance activities | None |

| **Important Identified Risk- Progressive multifocal leukoencephalopathy (PML) (all indications)** | |
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| Evidence for linking the risk to the medicine | PML is most frequently diagnosed in patients infected with HIV. Incidence rates in HIV-infected patients treated with antiretroviral therapy have been reported to be 0.06% in Switzerland, and 1.3 cases per 1,000 person-years in Denmark (Amend *et al*. 2010).<br>Incidence rates estimated from a retrospective observational cohort derived from a large US health insurer database have been published for PML in patients without HIV for the period January 2000 to June 2008 (Amend *et al*. 2010). There were 138,469 patients with autoimmune diseases, 25,706 with NHL or CLL, and 8,778 with transplants. Among 699 people who met screening criteria for potential PML, 89 had a diagnosis of PML. Medical records were sought for 24 patients without HIV, and six had confirmed PML upon |

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| | review of medical records. The PML incidence rate was 2.4 (95% confidence interval [CI] 0.06–13.18) in the systemic lupus erythematosus cohort and 10.8 (95% CI 0.27–60.39) in the autoimmune vasculitis cohort per 100,000 person-years; this rate estimate was based on one case reported in a patient with Wegener's granulomatosis (GPA). In the NHL and CLL cohorts, the incidence rate was 8.3 (95% CI 1.71–24.24) and 11.1 (95% CI 0.28–61.74) per 100,000 person-years. The incidence rate among patients with bone marrow transplantation was 35.4 per 100,000 person-years (95% CI 0.90–197.29). There were no cases of PML among patients with rheumatoid arthritis (95% CI 0.0–2.24), multiple sclerosis (95% CI 0.0–5.24), Sjögren's disease (95% CI 0.0–21.84), or solid organ transplantation (95% CI 0.0–26.81).<br><br>In an estimate derived from a hospital discharge sample in the USA (20% of hospitalisations), the cumulative incidence of PML in rheumatoid arthritis was 1 per 100,000 admissions (Molloy ES *et al.* 2008). When patients with defined risk factors for PML were excluded, the incidence of PML in rheumatoid arthritis patients was 0.4 per 100,000 admissions.<br><br>There are a number of case reports of PML in the global literature in patients with GPA/MPA. In a review covering the years 1992 to 2010 there were five published reports of PML in patients with GPA, none of whom had been treated with rituximab (Ettinger J *et al.* 1989; Choy DS *et al.* 1992; Morgenstern LB *et al.* 1995; Pagnoux C *et al.* 2003; Wang Y *et al.* 2004). All five patients had received cyclosporin and prednisone.<br><br>Studies reporting the incidence of PML among patients with haematological malignancies are limited. Carson *et al.* (2009) referred to a small number of studies assessing the incidence of PML namely, one population-based study that estimated an incidence of PML of 0.07% based on three cases of PML identified in HIV-negative patients with haematological malignancies over 11 years in Manitoba, Canada (Power *et al.* 2000). A higher incidence of PML of 0.52% was reported in another study in patients with CLL; these patients were treated with fludarabine (Gonzales *et al.* 1999). Carson *et al.* (2009a) concluded that estimating the risk of PML attributable to the underlying malignancy as opposed to immunosuppression due to treatment was complicated by the rarity of the disease and few large trials from which incidences can be determined prospectively. Fludarabine was seen as the drug most closely associated with PML possibly due to the effect of T-cell depletion (Garcia-Suarez *et al.* 2005). Carson *et al.* (2009) also reported that it is not possible accurately to estimate the incidence of PML associated with rituximab among persons with haematological malignancies because of incomplete reporting of PML cases and incomplete data on the number of unique patients with lymphoid malignancies who have |

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| | received rituximab. It has also been emphasised that the epidemiology of PML in the setting of lymphoid malignancies has changed in recent years; before 1990, most PML cases occurred in Hodgkin's disease. Whereas in recent years, with the development of purine analogues, haematopoietic stem cell transplantation, and rituximab, most PML cases occur in non-HIV-infected persons with NHL or CLL (Garcia-Suarez *et al*. 2005). As rituximab is routinely added to the treatment for haematological malignancies, the contribution of confounding factors to the development of a rare disease such as PML is difficult to estimate.<br><br>Bower *et al.*(1997) reviewed B-cell CLL patients seen at the Mayo Clinic from 1987 to 1991 for neurological complications including PML. Among 962 CLL patients there were five cases of PML (0.5%) and three further unconfirmed cases. The incidence rate of confirmed PML was estimated to be 108.5 per 100,000 patient-years (95% CI 35.2-253.1 per 100,000 patient-years). The authors noted that their study may overestimate the incidence of PML in the general CLL population as the Mayo Clinic is a tertiary care centre, and therefore only receives more severe patients.<br><br>A single-centre study from Italy reported the incidence of PML amongst 976 subjects with NHL diagnosed between 1994 and 2008 (Tuccori *et al.* 2010). No case of PML was identified amongst 459 subjects that had not been treated with rituximab (Incidence Rate [IR] 0 per 100,000 person-years, 95% CI 0-180). There were five reports of PML among 517 subjects with NHL treated with rituximab (IR 240 0 per 100,000 person-years, 95% CI 100-560). The incidence rates should be interpreted with caution due to possible detection bias due to the use of historical controls, and the effect of publicity concerning the association between PML and rituximab treatment. |
| Risk factors and risk groups | • HIV/AIDS (especially with CD4+ lymphocyte counts less than 200 cells/µL)<br>• immunosuppressive medications (such as haematopoietic/solid organ transplant recipients), including steroids<br>• haematological malignancies<br>• treatment with chemotherapy drugs (especially fludarabine)<br>• treatment with natalizumab or efalizumab<br>• autoimmune disorders<br>• tuberculosis |

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| Risk minimisation measures | Routine risk minimisation measures<br>SmPC section 4.4<br>SmPC section 4.8<br>Legal status: Restricted medical prescription<br>Additional risk minimisation measures:<br>Non-oncology indications only<br>– Patient alert card |
| Additional pharmacovigilance activities | None |

## *II.C Post-authorisation development plan*

### II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Truxima/Blitzima.

### II.C.2 Other studies in post-authorisation development plan

There are no studies required for Truxima/Blitzima.

# PART VII: ANNEXES

## List of Annexes

## ANNEX 4 Specific adverse drug reaction follow-up forms

Not applicable.

## ANNEX 6 Details of proposed additional risk minimisation activities

### Approved key messages of the additional risk minimisation measures

Non-oncology indications:

The MAH must ensure that all physicians who are expected to prescribe Truxima/Blitzima are provided with the Patient Alert Card.

The Patient Alert Card for Truxima/Blitzima in non-oncology indications should contain the following key elements:

- The need to carry the card at all times and to show the card to all treating health care professionals
- Warning on the risk of infections and PML, including the symptoms
- The need for patients to contact their health care professional if symptoms occur

The Patient Alert Card must be agreed with the National Competent Authorities prior to distribution.