WHO-PQTm SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Truxima[1] - 500mg concentrate for solution for infusion
Manufacturer of Prequalified Product:	Celltrion, Inc., Plant II (CLT 2) 20, Academy-ro 51 beon-gil, Yeonsu-gu, Incheon, 22014, Republic of Korea
Active Pharmaceutical Ingredient (API):	Rituximab
Pharmaco-therapeutic group (ATC Codes):	Antineoplastic agent, monoclonal antibody (L01XC02)
WHO recommended therapeutic indication:	diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma

1. Introduction

Truxima is an anti-CD20 chimeric immunoglobulin G1 (IgG1) monoclonal antibody.

The production process follows a standard procedure for monoclonal antibodies production; starting from the thawing of WCB followed by several cell expansion steps before final bioreactor production. Truxima is purified through a series of chromatographic (affinity and ion-exchange) and filtration steps, including dedicated viral inactivation steps (chromatography steps, low-pH treatment and nanofiltration). In-process control tests are sufficient to ensure the microbial/viral safety of the product, and consistent quality.

The prequalification of this product by the WHO Prequalification Team: Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely the "European Medicines Agency" (EMA http://www.ema.europa.eu/ema/) in line with the "WHO Guidelines on submission of documentation for the pilot procedure for prequalification of rituximab or trastuzumab approved by stringent regulatory authorities"[2].

Hence, no assessment of the data underlying this approval has been undertaken within PQTm. However, according to the above-mentioned guidelines, WHO requested additional data for the safe use of the product in regions relevant for prequalified products and this information is included in this section of the WHOPAR

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

[2] https://www.who.int/medicines/regulation/biotherapeutic_products/en/

2. Assessment of Quality

Product packaging and shipping

The assessment of the packaging and shipping of the product has been done according to the principles laid down in the WHO guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23), partially applicable also to biotherapeutics.

The Applicant provided data to demonstrate the maintenance of the required 2°C - 8°C temperature conditions for at least 120 hours between +30 °C and 0 °C ambient temperature, for 83 hours at +40.2°C, 62 hours at +48.6°C and for 44 hours at +60.1°C. Furthermore, shipping validation was performed to support product transportation from the labeling and packaging site to the warehouses. The shipping route for the validation studies has been determined from the worst perspective of the estimated shipping duration and distance from the manufacturer to the labeling and packaging site or the warehouse to cover the routine shipping procedures for commercial supply. All the validation results met the pre-defined acceptance criteria and the results demonstrate that drug product shipping procedure has been validated, in compliance with WHO requirements.

The Applicant also confirmed that the products are shipped through a direct route unless unavoidable, that the products are managed to arrive at the airport of final destination within 48 hours unless unavoidable and that in ordinary cases, the products are shipped during weekdays unless holiday shipping is specifically requested by the importer.

The Applicant provided evidence that temperature data loggers will be used for every shipment and that they will be programmed to show an alert on the device when exposed to temperatures outside the required range (2°C - 8°C).

The Applicant confirmed also that information and training required for the preparation of the transport, the container pick-up from container supplier, the product pick-up and loading, handover of the shipment to the airline, the transport, the delivery and the stopping of the data logger and the actions required in case of temperature deviation.

Arrangements for handling complaints and product recalls

The procedure for handling product quality complaints and product recalls submitted by the applicant provides details, among others, on the initial assessment of potential complaint criticality, root cause investigation process, established timeframe for the completion of the investigation process, definition of serious quality issues, established timelines for recall notification to National Medicines Regulatory Authorities and WHO, description of the recall arrangements and actions to put in place at the distribution level, as well as description of the periodical mock-recall for a product distributed in Low-Middle-Income-Countries (LMIC).

The applicant confirmed that the handling of complaints and recalls will also be clearly defined in the agreements or contracts between the manufacturer and the procurement agency, which manages the distribution of the medicinal product in LMIC.

Conclusion: the quality part of the dossier is accepted.

Pharmacovigilance - WHO PREQUALIFICATION-SPECIFIC ADDENDUM to the RMP

WHO assessed the latest SRA-approved Risk-Management Plan (RMP) and post-marketing safety reports together with a WHO PQ-specific addendum to the RMP according to the structure detailed on

the WHO-PQT website[3]

The WHO-prequalification-specific addendum to the RMP is reported below.

Conclusion: the pharmacovigilance part of the dossier is accepted.

[3] https://www.who.int/medicines/regulation/RMP_AddStructureDec2019-2.pdf?ua=1)

WORLD HEALTH ORGANISATION PREQUALIFICATION SPECIFIC ADDENDUM TO THE EU-RMP FOR CT-P10 (Truxima®)

1. Product information

Marketing Authorisation Holder	Celltrion Healthcare Co. Ltd
Product Name:	Truxima®
Active Ingredient(s):	Rituximab
Pharmaco-therapeutic Group (ATC Code):	Antineoplastic agents, monoclonal antibodies (L01X C02)
Indications for WHO PQ	Non-Hodgkin's lymphoma (NHL) For the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy. Maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy. Monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Truxima is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy. Chronic lymphocytic leukaemia (CLL) Truxima in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.
Posology for WHO PQ	Non-Hodgkin's lymphoma *Follicular non-Hodgkin's lymphoma*

	Combination therapy: The recommended dose of Truxima 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. Truxima should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable. Maintenance therapy: Previously untreated follicular lymphoma The recommended dose of Truxima used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (12 infusions in total). Relapsed/refractory follicular lymphoma The recommended dose of Truxima used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (8 infusions in total). Monotherapy: Relapsed/refractory follicular lymphoma The recommended dose of Truxima monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy is: 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks. For retreatment with Truxima 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. *Diffuse large B cell non-Hodgkin's lymphoma* Truxima 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. Dose adjustments during treatment No dose reductions of Truxima are recommended. When Truxima is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied. Chronic lymphocytic leukaemia Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are >25 x 10^9 /L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with Truxima to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome. The recommended dosage of Truxima 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 CT-P10 infusion.

2. Summary of Safety Concerns

For global harmonisation, safety concerns about Truxima for WHO PQ are aligned with those included in the latest approved version of the EU RMP for Truxima. In addition, local specific condition can be considerable and the local specific RMP could address to those at national level to ensure upon request of regulatory authorities. The applicant will assess the local healthcare settings and practice, infrastructure, epidemiology in the area where the product will be newly marketed, in comparison to the EU setting. It will contribute to identify any potential safety concerns which are newly arisen depending on the local specific condition.

List of safety concerns	
Important identified risks	Infusion-related reactions Infections including serious infections Progressive multifocal leukoencephalopathy (PML) Hepatitis B virus (HBV) reactivation

List of safety concerns	
Important potential risks	Off-label use in paediatric patients Administration route error
Missing information	Use during pregnancy or lactation

3. Pharmacovigilance Activities Specified for WHO PQ

The applicant will establish contact with a PV responsible person at the national PV centre or national regulatory authority (NRA) of the country for all safety issues in order to ensure the systematic and effective functioning of PV activities through regular reporting of ADRs. The applicant will appoint a designee/designees in countries where a PV responsible person is not present according to the local regulation. It is expected that designees to perform the majority of their functions within the bounds of that area of responsibility.

A flow chart summarising how the applicant currently communicates with NRAs is presented in Figure 1 and it will apply to the same for applicable countries. These communication flow can be modified in accordance with local regulations in NDA or procurement units after prequalification.

Figure 1. Flow chart summary

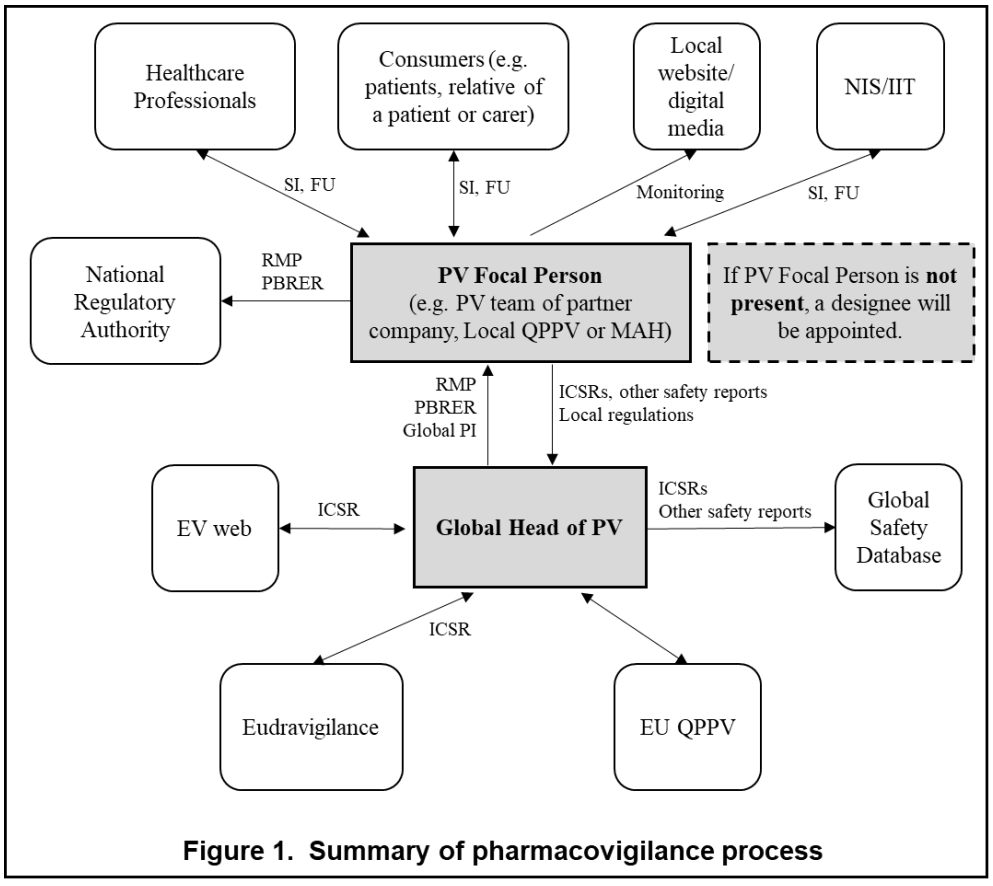

Figure 1. Summary of pharmacovigilance process

(SI = Safety Information; AEs, ADRs, quality complaints, events of special interest (e.g. Reports of overdose, abuse/misuse, off-label use, medication error or occupational exposure), FU= Follow-up, PI = Product Information, NIS/IIT=Non-Interventional Study/Investigator-Initiated Trial)

3.1 Routine Pharmacovigilance Activities

All newly acquired safety information will continue to be actively monitored in accordance with Good Pharmacovigilance Practices, including regular review and evaluation of cumulative data. Communication with regulatory agencies will occur through submission of individual expedited reports, and periodic pharmacovigilance reports, as needed for newly detected adverse reactions that might materially influence the benefit-risk assessment of Truxima. The purpose of routine pharmacovigilance activities is to monitor outcomes and trends in incidence and to implement appropriate risk minimisation activities, if required.

Collection of Individual Case Safety Reports (ICSRs) – The MAH has been collecting ICSRs via solicited and unsolicited reporting such as spontaneouse cases, literature. In accordance with the regulations of each Regulatory Authority, expedited reports are submitted to the Regulatory Authority in a given timeline.

Signal Detection – The MAH has been using a validated signal detection system. The MAH also updates on safety-related regulatory actions taken by other regulatory authorities, i.e. EMA, US FDA.

Periodic Benefit Risk Evaluation Report (PBRER) – Safety information about CT-P10 will be generated periodically in scheduled PBRERs. In the PBRER, all spontaneous and clinical cases reported during the review period are discussed in detail under the relevant SOC. Periodic safety update reports (PSURs) will be available and submitted in accordance with the each national requirements. In addition, the applicant will discuss with the NRA on harmonisation of PSUR frequency agreed with the Stringent Regulatory Authority (SRA) in order to comply with the ICH E2C guideline.

Specific adverse reaction follow-up questionnaires – In order to obtain structured information on reported suspected adverse reactions of the following risks, specific adverse reaction follow-up questionnaires has been used for following risks:

<u>Important identified risks</u>

- Progressive multifocal leukoencephalopathy (PML)

<u>Important potential risks</u>

- Off-label use in paediatric patients

The proposed routine pharmacovigilance activities are adequate to be implemented in not only EU countries but also low-and middle-income countries (LMIC).
Current clinical practices, healthcare settings and infrastructures may vary between the EU countries and LMIC. However, no matter where patients receive Truxima, it should be administered by healthcare professionals who are experienced in the use of this treatment (see the EU SmPC *4.2 Posology and method of administration*). They should monitor the patients closely while giving the medicine and check if the patients get any adverse reaction. They are asked to report any suspected adverse reactions. The package leaflet of Truxima includes the message for the safe use of Truxima.

In addition, the package leaflet provides information about how to report adverse reactions. Based on collected reports of adverse reactions, the MAH conducts the proposed routine pharmacovigilance activities.

Since adverse reactions are reported by healthcare professionals, the information collected in LMIC is as reliable as that of EU countries. Also, the MAH will make follow-up attempts to identify omitted information if necessary.

3.2 Additional Pharmacovigilance Activities

The study in the development programme for CT-P10 in oncology indications (Study CT-P10 3.4) has not completed the planned observation period at the data lock point for this RMP.

The applicant proposes to use the safety data derived from the ongoing clinical development study as the sole source of data, in addition to routine pharmacovigilance measures, to allow a more confident assessment of the safety profile of CT-P10, based on the assumption that therapeutic similarity between CT-P10 and the reference product has been, and will continue to be, satisfactorily demonstrated in all clinical studies in the development programme.

The study from the ongoing CT-P10 clinical development programme that is intended to fulfil this purpose is described below.

	Description of activity (or study title if known)	**Milestone(s)**	**Due Date(s)**
1	PROTOCOL NUMBER CT-P10 3.4 A Phase 3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Compare Efficacy and Safety between CT-P10 and Rituxan® in Patients with Low Tumour Burden Follicular Lymphoma	Protocol submission	Not applicable
		Study start (FPFV)	09 Nov 2015
		Study finish (LPLV)	Up to 7 months: 4Q 2018 Up to 27 months:2Q 2020
		Final report	Estimated CSR completion (up to 7 months): 1Q/2020 Estimated CSR completion (up to 27 months): 4Q/2021

The applicant will undertake an assessment at national level whether any additional pharmacovigilance activities are required to address local specificities that may change the benefit/risk profile defined within the SRA settings upon discussion with the NRA, in the local specific RMP. Local specificities could include epidemiology (e.g. infection), healthcare infrastructure, clinical practice, social, economic and other.

4. Risk Minimisation Activities Specified for WHO PQ

4.1 Routine and Additional Risk Minimisation Activities

Following routine risk minimisation measures are proposed based on the EU Summary of Product Characteristics (SmPC) which is company core data sheet.

Proposed routine and additional risk minimistation measures are harmonised with the EU RMP.

Safety concern	Proposed routine risk minimisation activities	Proposed additional risk minimisation activities
Identified risk – Infusion-related reactions	EU SmPC section: 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Identified risk – Infections including serious infections	EU SmPC section: 4.2 Posology and method of administration 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Identified risk – Progressive multifocal leukoencephalopathy (PML)	EU SmPC section: 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Identified risk – Hepatitis B virus (HBV) reactivation	EU SmPC section: 4.3 Contraindications. 4.4 Special warnings and precautions for use 4.8 Undesirable effects	None
Potential risk – Off-label use in paediatric patients	EU SmPC section: 4.1 Therapeutic indications 4.2 Posology and method of administration	None
Potential risk – Administration route error	EU SmPC section: 4.2 Posology and method of administration	Physician information
Missing information - Use during pregnancy or lactation	EU SmPC section: 4.6 Fertility, pregnancy and lactation	None

The proposed routine risk minimisation measure is adequate to be implemented in not only EU countries but also low-and middle-income countries (LMIC).

Upon assessment, taking into consideration how familiar healthcare professionals are with the product, local clinical practice and healthcare setting/infrastructure, the applicant will implement additional risk minimization measures at a national level if considered necessary for example non-promotional educational material.

The applicant will ensure accessibility of SmPC and where relevant, non-promotional purpose educational materials to HCPs considering healthcare setting/infrastructure in that country. The education materials will cover that the product is only used where there are adequate facilities to implement the risk management measures (RMMs), e.g. for the important identified risk ‘acute infusion related reactions’ with rituximab, close supervision by an experienced HCP is required in an environment where full resuscitation facilities are immediately available. This could take the form of a

checklist for each of the safety concerns and the proposed actions that may be required. Implementation in national level will subsequently discussed with the NRAs.

4.2 Risk Minimisation Activities Monitoring

The applicant will monitor whether the risk minimisation measures are being implemented and whether they are effective via methodology introduced in the EU RMP, signal detection.

5. Product traceability

The essential information presented in the packaging material are provided in Annex III of EU SmPC as well as 2D barcode and serial number. Also the tertiary packaging material contains information, such as Product Name, Lot No. Quantity, Storage condition, Manufacturer and Expiry date of drug product. The applicant keeps tracking the history of drug product lot release, generating a document including a lot number, the destination of shipments, etc. This allows the applicant to track the drug product lot from manufacturing to distribution.

As EU SmPC of Truxima® is submitted for WHO PQ as product information, product traceability can be improved by recording the tradename and batch number of the administered product and it is stated in the EU SmPC section *4.4 Special warnings and precautions for use* as follows:

> **4.4 Special warnings and precautions for use**
>
> In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Any healthcare professional can access the information which are written on the secondary packaging of the product, so that healthcare professionals easily record relevant information in the patient file or the individual case safety reports. The applicant will try to emphasize the importance of providing the tradename and batch number when reporting adverse events in order to ensure recording of this information in the patient's file.

In addition, the applicant is collecting the tradename and batch number via ICSR reporting to monitor product traceability. If any initial ICSRs received does not include either the tradename or batch number, follow-up request is performed to try and obtain this information.

Product traceability system for Truxima® can be amended in accordance with local regulation by NRA or procurement unit after prequalification.

6. Conclusion

A commitment from the Applicant that they acknowledge healthcare settings and infrastructure may vary between countries, and following prequalification, they will evaluate the adequacy of the safety concerns, Pharmacovigilance (PV) activities, risk minimization measures (RMMs) and traceability of the product at a national level. Furthermore, that the Applicant will implement sufficient PV activities, RMMs and product traceability following product prequalification even if differences, compared to SRAs, in healthcare settings and/or infrastructure are found at a national level.