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:	Ontruzant [1]
Manufacturer of Prequalified Product:	Biogen (Denmark) Manufacturing ApS, Biogen Allé 1, 3400 Hillerød, Denmark
Active Pharmaceutical Ingredient (API):	Trastuzumab
Pharmaco-therapeutic group (ATC Codes):	Antineoplastic agent, monoclonal antibody (L01XC03)
WHO recommended therapeutic indication:	early stage HER2 positive breast cancer or metastatic HER2 positive breast cancer

1. Introduction

Ontruzant (trastuzumab) is a recombinant DNA-derived, humanized monoclonal antibody (IgG1 kappa) that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. Ontruzant consists of 1,328 amino acids and has a molecular weight of approximately 148 kDa. Trastuzumab is comprised of two identical HCs and two identical LCs. One N-linked glycosylation site is located at Asparagine-300 on each heavy chain. There are no O-linked glycosylation sites.

After thawing of the Working Cell Bank (WCB) vial, the culture is serially expanded in cell mass and volume for inoculation into the production bioreactor. The cell culture fluid is subsequently purified through a series of chromatographic steps, virus inactivation and filtration steps.

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

2. Assessment of Quality

[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/

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 96 hours during shipment when the shipping container battery is continuously charged. The data confirms a minimum of 96 hours during shipping with the temperature maintained at 2°C - 8°C, in compliance with WHO requirements.

Furthermore, the Applicant has confirmed that if shipping is required in extremely hot areas a Temperature Controlled Vehicle (TCV) will be used in addition to the shipping container for product shipment, to further ensure the maintenance of the required 2°C - 8°C temperature within the shipping container. Furthermore, if required, temperature records of TCV can be collected and provided for every shipment.

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 handling the temperature monitoring device at the packing/sending sites will be provided, including preparation, operation and placement of the temperature monitoring device (TMD) in the shipments. Written instructions for reading the TMD data and mechanism for advising of any excursions will be provided to the person receiving the shipment.

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 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)

Annex 13 WHO Prequalification Specific Addendum

13.1 Introduction

Ontruzant is indicated for metastatic breast cancer, early breast cancer, and metastatic gastric cancer in the EU. Only the breast cancer indications are invited for WHO prequalification program. It is administered intravenously at a dose of 6 mg/kg trastuzumab once every 3 weeks after 8 mg/kg loading dose or 2 mg/kg weekly after 4 mg/kg loading dose.

The proposed safety concerns and respective PV activities and risk minimization measures for this application are summarized below.

Safety concern	Risk minimization measures*	Pharmacovigilance activities
Important identified risks		
Cardiac Dysfunction	<Routine risk minimization measures> - SmPC section 4.4 and 4.8 where advice is given on cardiac function monitoring - PL section 2 and 4 where recommendation for heart function monitoring and early signs and symptoms of cardiac dysfunction are included - Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> - AE follow-up form for Cardiac adverse events <Additional pharmacovigilance activities> - SB3-G31-BC-E
Administration-Related Reactions (ARRs)	<Routine risk minimization measures> - SmPC section 4.2, 4.4 and 4.8 where signs and symptoms and advice on premedication and treatment for ARRs are given - PL section 4 where signs and symptoms of ARRs are given - Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> - AE follow-up form for ARR
Haematotoxicity	<Routine risk minimization measures> - SmPC section 4.8 - PL section 4 where signs and symptoms of haematotoxicity are given - Prescription-only medication	None
Oligohydramnios	<Routine risk minimization measures> - SmPC section 4.6 and 4.8 - PL section 4 where signs and symptoms of oligohydramnios are given - Prescription-only medication	None
Pulmonary Disorders	<Routine risk minimization measures> - SmPC section 4.3, 4.4 and 4.8 where the risk of pulmonary disorders and caution on patients at higher risk are given - PL section 4 where signs and symptoms of pulmonary disorders are given - Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> - AE follow-up form for Interstitial lung disease
Important potential risks		
Infections	<Routine risk minimization measures> - SmPC section 4.8	None

Safety concern	Risk minimization measures*	Pharmacovigilance activities
	- PL section 4 where signs and symptoms of infections are given - Prescription-only medication	
Medication Error	<Routine risk minimization measures> - SmPC section 4.2 - PL section 3 where recommendations to prevent medication error are given - Prescription-only medication	<Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection> - AE follow-up form for Medication Errors
Missing information		
Treatment in Male patients (Breast Cancer Indications Only)	<Routine risk minimization measures> - Prescription-only medication	None

*Ontruzant package will contain the product label, which ensures healthcare professional's access to the product information. The routine risk minimization measures will be included in the respective sections of the local labels accordingly.

The Applicant acknowledges that the healthcare settings and infrastructure may vary between countries, and following prequalification, the Applicant will employ and evaluate the adequacy of the safety concerns, PV activities, risk minimization measures and traceability of the product at a national level. The Applicant will implement sufficient PV and risk minimization measures following product prequalification even if differences in healthcare settings are found at a national level.

13.2 Summary of the methodological concepts that will be employed at a national level for country specific RMPs

Safety concerns

The Applicant is aware of potential differences in the healthcare setting and local specificities that may change the benefit-risk profile. Before new market entry, the Applicant will assess the local healthcare settings, infrastructure, PV alliance model and any local studies and identify potential gaps that may trigger new safety concerns at the local level. Such assessment will be done in comparison with the EU label to detect potentially different factors such as indications, posology, concomitant medications, compounding and drug administration environment that could differ by local practice. The evaluation results will determine if any different or new safety concerns could arise and if additional PV activities or risk minimization measures other than those listed in the table above are necessary. Then, the Applicant will implement them as appropriate and assess the safety concerns in accordance with the PV activities that will be committed in local specific RMPs including continuous safety database monitoring and signaling activities.

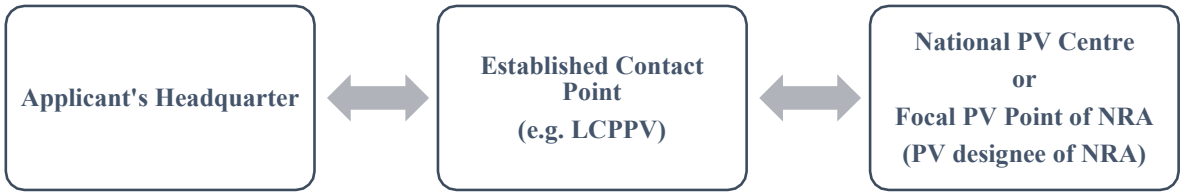
Pharmacovigilance activities

For the countries in which the Applicant's product is approved, adequate PV system including the communication route with a PV focal person at the national PV centre or national regulatory authority (NRA) of the country will be established in accordance with local and global requirements such as Local Contact Person for PV (LCPPV) or local affiliate.

In case of entry to new countries, the Applicant will assess communication plans based on the local requirements. To select the adequate contact point, the Applicant considers specific checkpoints such as 24/7 availability and local language skills. Based on the assessment result, the Applicant will establish necessary contact with a PV focal person at the national PV centre or NRA of the country.

In specific countries where the national PV centre or the focal PV point is not present, the Applicant will communicate with the regulatory authority (RA) to establish a communication route or designated contact point for safety issues. If the adequate contact information of designee is notified, the Applicant will contact the designee of the NRA through the LCPPV or the local affiliate.

The settled communication route with a PV focal person at the national PV centre or NRA will be used to communicate or report any safety concerns/queries such as a new safety issue or validated signal considered by the Applicant.



To evaluate PV requirements regarding ADR reporting and follow-up at a national level before marketing authorization application or launch of a product, the local requirements and system will be assessed by the Applicant with specific checkpoints such as case intake, case processing, case reporting, safety database, and communication plan.

Through the assessment, the Applicant will verify that critical procedures of ADR reporting and follow-up at a national level are aligned with the Applicant's central PV system even though there will be different healthcare settings and infrastructure between countries. Based on the assessment result, the Applicant will establish necessary PV procedures at a national level, and appropriate ADR reporting and follow-up will be conducted.

Local specificities considered for the assessment of a need for additional PV activities will cover epidemiology (e.g. infection), healthcare infrastructure, clinical practice, social and economic status, etc., as appropriate.

The Applicant is currently developing Periodic Safety Update Reports in accordance with the European Union reference dates (EURD) list. Once Ontruzant is approved, it will be submitted to NRAs as well in accordance with the national requirements.

Risk minimization measures

Upon assessment, taking into consideration how familiar healthcare professionals are with the product, current clinical practice and the healthcare setting/infrastructure in that country, the Applicant will implement additional risk minimization measures if considered necessary. It would include non-promotional educational material or a checklist to ensure that the product is used only in the settings with adequate condition to implement adequate risk minimization measures. For example, regarding some of the safety concerns of

Ontruzant (cardiac dysfunction and pulmonary disorders) that can be recognized only by additional effort to detect them and that needs to be managed in an experienced way, the Applicant would provide non-promotional educational material as assisting tool so that caring physician can understand the adverse events and determine the following actions when the adverse event occurs.

Such educational materials for healthcare professionals could help them to understand and appropriately manage adverse events as well as be aware of the importance of safety reporting and how to report such safety issues. In addition, risk-minimization measures to assist healthcare professionals to calculate the dose and schedule the dosing interval and follow-up (e.g. anticancer therapy timetable) would be another example. If healthcare professionals are not familiar with trastuzumab and advanced healthcare infrastructure is not available, the assisting tool could help healthcare professionals to minimize the risk from the difference in healthcare setting by allowing them to adhere standard practice.

Continuous AE intake and signaling activities will allow the Applicant to monitor any unusual safety issues at a national level. If different issues are identified at a national level compared to what has been identified in the SRAs, appropriate risk minimization activities will be implemented, and their effectiveness will be assessed periodically by following up the AE reporting rate of the respective safety concern.

Product traceability

During the manufacturing stage, a specific lot number is given to a batch of product for identification of the drug substance and drug product. Furthermore, as long as the brand name and lot number are documented in the patient chart, follow-up is possible in case of any product safety issue. In order to collect such information, all package label should include a prominent statement that the brand name and batch number should be clearly recorded in the patient file. In order to further aid product traceability, peel-off of labels will be used for Ontruzant, detailing the brand name and batch number, to be placed in the patient file after administration.

Communication to healthcare professionals should emphasize the importance of providing the brand name and batch number when reporting suspected adverse reactions. And if an ADR report is received without details of the brand name and/or batch number, a follow-up request would be performed to try and obtain this information.

Most of the product dissemination in low- and middle-income countries will take the form of one of the following two scenarios.

First, if trastuzumab is commercialized via marketing partners, its distribution will be tracked in every possible detail from manufacturer to the final delivery site, such as clinics or hospitals. Second, if the drug is dispensed through an institute or agency, including procurement agencies, as long as the lot number is documented at the final destined hospital, the product can be traced, and any necessary drug information will be provided once requested to the Applicant.

Although low- and middle-income countries may have different healthcare settings, the supply chain for trastuzumab will be nearly consistent. Trastuzumab is prescribed and administered in a hospital setting as it is given intravenously, so the possibility of deviation or medication error from patient use is very low. In other words, the Applicant believes

that product traceability, which is one of the significant factors for PV, will be feasible as the distribution channel ends at a hospital, and drug is administered by a healthcare professional.