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:	Ogivri [1]
Manufacturer of Prequalified Product:	Name and address of the manufacturer of the biological active substance: Biocon Biologics Limited Special Economic Zone, Plot Nos. 2, 3, 4 & 5, Phase-IV, Bommasandra-Jigani Link Road Bommasandra Post, Bengaluru - 560 099 India
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

Ogivri (trastuzumab) is a recombinant deoxyribonucleic acid (DNA)-derived humanized monoclonal antibody directed against human epidermal growth factor receptor type 2 (HER2). It belongs to the immunoglobulin G subclass 1 kappa isotype and contains human framework regions with the complementary-determining regions of a murine antibody (4D5) that binds to HER2. It is expressed in Chinese Hamster Ovary (CHO) cell line and contains 2 identical heavy chains (HCs) and 2 identical light chains (LCs). Both HCs contain an oligosaccharide chain linked to protein at Asn300.

The prequalification of this product by the WHO Prequalification Team: Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely "Swissmedic" (https://www.swissmedic.ch) 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://extranet.who.int/prequal/sites/default/files/document_files/03_Pilot_PQ_anticancer_AbridgedPathway_Feb2020.pdf

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 during shipment when the shipping container battery is continuously charged. The study that has been performed indicates that the autonomy of the batteries (that will be charged initially and during the hold at airports) is sufficient to maintain the temperature at different steps of the shipment. Furthermore, in case of any delays during hold at airports, the shipment containers will be stored and plugged into power in the cold store (2-8°C)/refrigerated warehouse. The data are considered in compliance with WHO requirements.

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. Upon receipt of the product at destination site, the product will be received and inspected for any damage, and temperature data logger downloaded for assessment.

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 investigation process, established timelines for effective recall system and rapid alert, definition of the risk of the 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.

The applicant confirmed that the handling of complaints and recalls will also be clearly defined in the agreements or contracts between the manufacturer and relevant third parties.

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://extranet.who.int/prequal/sites/default/files/document_files/RMP_AddStructureDec2019-2.pdf

WHO Prequalification-specific addendum to the RMP

Introduction

1.1 Product Information

Product name:	**Ogivri**
Active ingredient(s):	Trastuzumab (trastuzumab-dkst in the U.S.A.)

1.2 Indications / Posology

In line with local requirements, countries will have product information and package leaflet to aid Healthcare Professionals and patients, respectively. As disclaimed in the Company`s Reference Safety Information (RSI), locally approved indications may differ. This procedure allows alignment with local recommendations/regulations and harmonisation with reference product.

Indications

Trastuzumab is indicated for the treatment of metastatic breast cancer, early breast cancer and metastatic gastric cancer in the EU. Only the breast cancer indications are invited for the WHO prequalification programme.

Posology and administration:

It is administered intravenously at a dose of 6 mg/kg trastuzumab once every 3 weeks after a loading dose of 8 mg/kg or 2 mg/kg weekly after a loading dose of 4 mg/kg.

1.3 Safety Concerns/Risk Minimisation Measures/Pharmacovigilance Activities

Safety specification, risk minimisation measures and pharmacovigilance activities, according to EU-RMP (version 3.1, 06-Feb-2020), is presented below:

Safety specification	Safety concern	Risk Minimisation Measures (RMM)	Pharmacovigilance activities (PVA)
Important identified risks *(an untoward occurrence for which there is adequate evidence of an association with the therapeutic product)*	**Cardiac dysfunction**	Routine RMM: PI, PoM, RmP. Additional RMM: None	Routine PVA including guided questionnaire. The company will closely follow the conclusions for Herceptin and will implement additional measures for this safety concern (cardiac toxicity) as needed. Additional PVA: None

Safety specification	Safety concern	Risk Minimisation Measures (RMM)	Pharmacovigilance activities (PVA)
	Administration-related reactions	Routine RMM: PI, PoM, RmP. Additional RMM: None	Routine PVA including guided questionnaire. Additional PVA: None
	Oligohydramnios	Routine RMM: PI, PoM, RmP. Additional RMM: None	Routine PVA including guided questionnaire. The company commits to perform follow-up activities of all pregnancy cases with its product globally to collect additional information on women exposed to Ogivri® during pregnancy. With regards to performing follow-up activities of all pregnancy cases exposed to Ogivri® within seven months prior to conception, the MAH foresees difficulties in identifying the patients but has introduced this time frame in the guided questionnaire and will address it where possible. Additional PVA: None
Important potential risks *(an untoward occurrence for which there is some basis for suspicion of an association with*	None	Not applicable	Not applicable

Safety specification	Safety concern	Risk Minimisation Measures (RMM)	Pharmacovigilance activities (PVA)
the therapeutic product)			
Missing information	**Safety of docetaxel 75 mg/m^2 versus 100 mg/m^2**	Routine RMM: PI, PoM, RmP. Additional RMM: None	Routine PVA including comparative presentation of safety data captured in the global safety database in Periodic Benefit-Risk Evaluation Reports. Additional PVA: None

PI = Product Information. PoM = Prescription only medicine. RmP = Restricted medical prescription.
The product information advises that therapy should be initiated and supervised by physicians experienced in the administration of cytotoxic chemotherapy.

The Applicant acknowledges that the healthcare settings and infrastructure may vary between countries, and following prequalification, they will evaluate the adequacy of the safety concerns, pharmacovigilance activities, risk minimization measures and traceability of the product at a national level. The Applicant will implement sufficient pharmacovigilance, risk minimization measures and product traceability following product prequalification if differences, compared to stringent regulatory authorities (SRAs), in healthcare settings and/or infrastructure are found at a national level.

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

1.4 Safety concerns

The applicant will undertake assessment at a national level to ensure that any additional safety concerns, if present, are identified based on local practices or specificities. The local practices or specificities that will be considered for the assessment will cover e.g. epidemiology, healthcare infrastructure, clinical practice, social and economic aspects.

1.5 Description of the Proposed Local Pharmacovigilance (PV) Activities

Mylan pharmacovigilance is a company-wide global concept spanning the whole life-cycle of the company`s medicinal products managed by Global Product Safety and Risk Management (PSRM). The system is used to fulfil legal tasks and responsibilities in relation to pharmacovigilance across the globe and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.
As outlined in the Pharmacovigilance System Master File (PSMF) and the PV Quality Manual, the company has robust PV system in place, which meets Good Pharmacovigilance Practices (GVP) and International Conference on Harmonization (ICH) requirements including but not limited to:

- maintaining of PSMF,
- urgent safety alert/ medical risk assessment,
- monitoring of safety triggers,
- Individual Case Safety Report management (including submission to National Competent Authorities, NCAs),

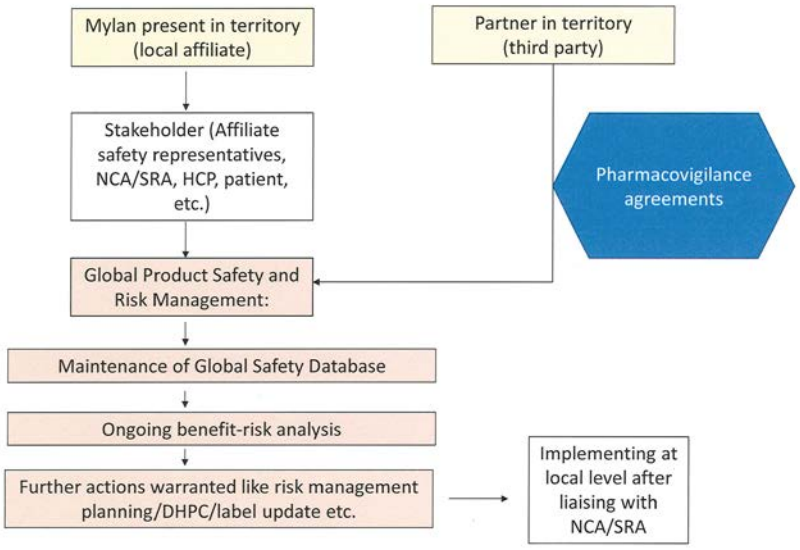
- aggregate report management (including submission to NCAs),
- periodic safety reporting (including submission to NCAs),
- safety signal management,
- risk management planning including additional pharmacovigilance and risk minimisation activities,
- post-authorization safety studies,
- managing requests from NCAs,
- creating and maintenance of Product Reference Safety Information and review of product information,
- PV Quality Management, archiving and training,
- PV inspections and corrective and preventive action management,
- establishing Pharmacovigilance Agreements where required with business partner,
- monitoring of key performance indicators.

Local activities are performed at local affiliate level. For the countries where Mylan does not have a local affiliate, Pharmacovigilance Agreements are in place with third parties to ensure that safety information from the territory reaches Mylan Global PSRM in appropriate time and quality. All processes are outlined in Standard Operation Procedures on Affiliate Pharmacovigilance System and Pharmacovigilance Agreements, as summarised in the PSMF.

Details of applicability of pharmacovigilance activities to regions are provided below:

(A) Routine PV Activities (rPVAs) *[applicable to <u>all</u> regions/countries]*

✓	Sharing information with National Competent Authority (NCA)/ Stringent Regulatory Authority (SRA) is established and outlined in below flow chart. Local safety information is shared with global Product Safety and Risk Management via affiliate safety representative or third-party business partners for evaluation. Upon analysis of global data if any actions like risk management planning or label updates are warranted, the same will be implemented at local level after liaising with NCAs.
✓	Timely update on significant safety issues that may influence the overall benefit-risk profile of the product, in line with local requirements
✓	Timely update on safety-related regulatory actions taken by SRAs (i.e., EMA, TGA, Health Canada, MHRA and US FDA), in line with local requirements



✓	Activities beyond ADR reporting and signal detection (targeted follow-up questionnaires), as further outlined below:

- Routine PVAs beyond ADR reporting and signal detection are summarized in the EU-RMP.
- Guided (targeted follow-up) questionnaires are established at the company to closely follow the following issues: i) cardiac dysfunction, ii) administration-related reactions, iii) pregnancy.
- Recording of brand name and batch number is implemented in all follow-up questionnaires for Mylan biosimilars (see Annex 4 of EU-RMP and Section 2.4, below).

In addition to these, the Applicant will establish contact with a PV focal person at the national PV centre or National Competent Authority (NCA) of the country for all safety issues. In countries where a focal PV point is not present, the Applicant will seek guidance from NCA on how to proceed.

Also, Periodic Safety Update Reports will be prepared and submitted in accordance with local/national requirement.

(B) Additional PV Activities (aPVAs)

As current routine pharmacovigilance activities are sufficient, aPVAs are not recommended as per EU-RMP.

The Applicant will undertake assessment at a national level, to see whether any additional pharmacovigilance activities are required to address local specificities. The local specificities that will be considered for the assessment of a need for additional pharmacovigilance activities will cover e.g. epidemiology, healthcare infrastructure, clinical practice, social and economic aspects.

1.6 Description of Proposed Risk Minimisation Measures (RMMs)

(A) Routine RMMs *[applicable to <u>all</u> regions/countries]*

✓	Legal status
✓	Pack size
✓	Provision of warnings and precautions in the Product Information/ label as approved by local health authority
✓	Provision of warnings and precautions in the package insert/ leaflet
✓	Timely safety updates to labelling and packaging

(B) Additional RMMs (aRMMs)

No aRMMs are mentioned in the trastuzumab EU-RMP. Routine RMMs including Product Information/ label, package leaflet and updates to labelling are considered to sufficiently cover safety concerns.

The Applicant will evaluate healthcare professionals` familiarity with the product/type of product (including accessibility to the Summary of Product Characteristics), current clinical practice and the healthcare setting/infrastructure at national level (see checklist below). If required, the Applicant will

seek guidance from PV focal person at the national PV centre or NCA on how to implement aRMMs (e.g. non-promotional educational material and that the product is only used where there are adequate facilities to implement the RMMs).

Check list for important safety concerns (important identified risks) and proposed actions that may be taken at national level:

Important safety concern	Aspect to be checked on national level	Checkbox (Y/N)
Cardiac dysfunction Administration-related reactions Oligohydramnios	Availability of SmPC	Y/N
	Accessibility of SmPC	Y/N
	Action to be initiated to ensure availability/accessibility of SmPC	Y/N
	Accessibility of guided questionnaires	Y/N
	Action to be initiated to ensure accessibility of guided questionnaires	Y/N
	Non-promotional material provided to HCPs	Y/N
	Treatment by experienced HCP	Y/N
	Action to be initiated to ensure treatment by experienced HCP	Y/N
	Close supervision of patients established	Y/N
	Action to be initiated to ensure close supervision of patients	Y/N

The applicant will monitor effectiveness of the risk minimisation measures via routine pharmacovigilance activities.

1.7 Traceability

The company acknowledges the need for traceability to be fully integrated in different healthcare settings and that infrastructure may vary between countries. A key requirement for pharmacovigilance of biologicals is the need to ensure continuous product and batch traceability in clinical use. Communication should emphasize the importance of providing the product name (or INN and name of the marketing authorisation holder) and batch number(s) when reporting suspected adverse reactions.

In line with international guidance on biological medicinal products, reporting drug name and batch number is mentioned in appropriate sections of OGIVRI Product Information/ labels and included in the product packaging. This information is therefore available to be recorded and reported at all levels in the supply chain from manufacturer release to prescription, dispensing and patient administration.

Trastuzumab will mainly be supplied in a hospital setting. A statement is presented in the local Product Information/ label reminding Healthcare Professional (HCPs) on the type of the medicinal product (biosimilar) and the need to clearly record both, the tradename and batch number in the patient's healthcare records. For the Mylan trastuzumab biosimilar, in all countries, no matter if middle or low income, INN and batch number can be found on the package.

According to international guidelines for the use of Biosimilars, Mylan has a process in place to cover the requirements of traceability and batch tracking. Pharmacovigilance activities for biosimilars such as trastuzumab follow established standard procedures laid down in global Standard Operating Procedures (SOPs). Collection of initial information such as Adverse events (AEs)/ Adverse Drug reactions (ADRs) as well as follow-up processes and requirements for additional information are described in global SOPs, explicitly mentioning biological medicinal products, where appropriate. All ADR reports for biological medicinal products including biosimilars are evaluated by a dedicated medical expert. Once missing information has been identified (e.g. reporting adverse events without indication of product name and batch number) or reported ADR would benefit from further investigation (i.e. immunogenicity report), send out of follow-up questionnaires to HCPs will be initiated, together with a "biologic-specific cover letter" mentioning importance of reporting batch number and product name for ADR reporting for biosimilars and importance of reporting suspected ADRs even if already listed in the product information.
At Mylan, immunogenicity follow-up forms are designed to collect information on all biological medicinal products administered to an individual in the past and current to support assessment of immunogenicity-related effects taking previous treatment into consideration.

In line with global guidance, a summary of relevant information on the batches delivered during Periodic Safety Update Report (PSUR) reporting period will be included in PSURs where relevant for interpretation of safety data. Following a significant change in manufacturing process, PSURs will specifically evaluate reports and any other information that might indicate a new clinical risk related to a process change. The required data on batch-specific exposure patterns will support each evaluation. This will be presented in the context of the specific concern that is included in any updated safety specification of the RMP.
PSURs will be submitted as per national requirements.

In conclusion, the Company performs diligent follow up on global level to obtain trade name and batch number to distinguish the report of the Applicant's product, reference product or other related products and to identify batch-related issues.

1.8 Additional Information

To list the supporting documents enclosed in this application and to provide other comments (if any)

The following documents are enclosed in the application:

- Recent version of the EU-RMP (procedure EMEA/H/C/0014196, version 3.1, 06-Feb-2020)
- Approved EU Summary of Product Characteristics (SmPC)

REVISION HISTORY

WHO-PqSARMP-OGIVRI-1.2