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 and 2 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Ituxredi[1] 100 mg/10 mL concentrate for solution for infusion
Manufacturer of Prequalified Product:	Dr. Reddy's Laboratories Ltd. Biologics, Survey No. 47 & 44 (Part) Bachupally Village, Bachupally Mandal Medchal-Malkajgiri District, Pincode 500090 Telangana State, India.
Drug substance(s):	Rituximab
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agent, monoclonal antibodies, CD20 inhibitors (L01FA01)
WHO recommended therapeutic indication:	Diffuse large B-cell lymphoma, chronic lymphocytic leukaemia and follicular lymphoma.

1 Introduction

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. Rituximab exerts its antineoplastic effect by suppressing the uncontrolled growth of immune B-cells, i.e., by inhibiting CD20 antigen on B lymphocytes and recruiting immune effector functions that mediate B lymphocyte lysis.

Rituximab's safety and efficacy profiles in oncology are well established, based on extensive clinical experience in the treatment of diffuse large B-cell lymphoma, follicular lymphoma and chronic lymphocytic leukaemia.

Ituxredi is biosimilar to MabThera (Roche).

Rituximab, the drug substance of Ituxredi, is produced by cell suspension culture in Chinese hamster ovary cells. It is then purified by chromatography and filtration, including specific viral inactivation and removal procedures.

The finished product is a clear to opalescent, colourless to yellowish concentrate for solution for infusion, containing 100 mg or 500 mg of rituximab drug substance. Other ingredients are sodium citrate, citric acid, polysorbate 80, sodium chloride and water for injections (WFI). Ituxredi 100 mg and 500 mg concentrate for solution for infusion is supplied in 10 mL or 50 mL clear type I vials respectively. Ituxredi is supplied in packs of 1 or 2 vials.

[1] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

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 (https://www.ema.europa.eu/en), 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

Product packaging and shipping

The assessment of the packaging and shipment process of the rituximab drug product has been conducted in accordance with WHO principles for the international transport of temperature-sensitive pharmaceuticals. The applicant submitted performance validation data for the shipping container. This container was tested under simulated summer and winter conditions based on ISTA 7D temperature profiles, demonstrating that it can reliably maintain internal temperatures between 2°C and 8°C for a minimum of 116.59 hours (summer) and 120 hours (winter), even under extreme ambient conditions ranging from –12.2°C to 41.5°C.

Additional real-world transport validation data confirmed that internal temperatures remained within the required range during transit, with only brief, non-impactful deviations. Calibrated data loggers placed at defined locations in each shipment continuously recorded temperature data at 10-minute intervals. Upon arrival, all containers and product units were inspected, with no physical damage or deviation in quality attributes observed.

A comprehensive quality risk assessment has been provided, including a failure mode and effects analysis (FMEA), addressing potential risks such as temperature excursions, handling errors, data logger malfunction, and environmental exposures. Stability data were used to define acceptable short-term excursions.

A broader evaluation of cold chain transport covering 158 international shipments, including rituximab, further supports the robustness of the packaging and logistics system.

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 product defects/serious quality issues definition, investigation process, process of recalls, established timelines for recall notification to National Medicines Regulatory Authorities and WHO, recall arrangements and actions to put in place at the distribution level as well as description of the annual mock-recall.

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

Stability of the product

The approved shelf-life for unopened Ituxredi 100 mg/10 mL concentrate for solution for infusion is 36 months when stored at 2°C to 8°C.
Diluted medicinal product

• After aseptic dilution in sodium chloride solution

[2] https://extranet.who.int/prequal/sites/default/files/document_files/03_Pilot_PQ_anticancer_AbridgedPathway_Feb2020.pdf

The prepared infusion solution of Ituxredi in 0.9% sodium chloride solution is physically and chemically stable for 60 days at 5±3°C and 30 days at 25±2°C.

• After aseptic dilution in dextrose solution

The prepared infusion solution of Ituxredi in 5% dextrose solution is physically and chemically stable for 48 hours at 2°C - 8°C and 25±2ºC.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C

Conclusion: The quality part of the dossier is accepted.

3 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

Risk Management Plan Addendum for WHO Prequalification

Part 1: General Product Information

1. Brand name	ITUXREDI (in European Union)	
2. Active substance, Strength, Dosage form	Rituximab, 100 mg/10mL (10 mg/mL), concentrate for solution for infusion	
3. Pharmacotherapeutic group and Anatomical Therapeutic Code (ATC):	Antineoplastic agents, monoclonal antibody; ATC: L0lFA0l.	
4. Marketing authorization holder (of Ituxredi in European Union)	Reddy Holding GmbH, Kobelweg 95, Germany.	
5. Details of Responsible Person for Pharmacovigilance (RPPV) (name, designation, email, telephone number)	Dr. Chetan Karoo Head of India and EM QPPV, Pharmacovigilance Dr. Reddy's Laboratories Ltd., Hyderabad, India. chetankaroo@drreddys.com	
6. Indications	*Non-Hodgkin's lymphoma (NHL)* • Rituximab is indicated for the treatment of previously untreated adult patients with stage III-IV follicular lymphoma in combination with chemotherapy. • Rituximab maintenance therapy is indicated for the treatment of adult follicular lymphoma patients responding to induction therapy. • Rituximab monotherapy is indicated for treatment of adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. • Rituximab is indicated for the treatment of adult patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy. • Rituximab 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).	

	Chronic lymphocytic leukaemia (CLL) • Rituximab in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data is available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patient's refractory to previous rituximab plus chemotherapy.
7. Posology	Non-Hodgkin's lymphoma Follicular non-Hodgkin's lymphoma *Combination therapy*: 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 (BSA) per cycle, for up to 8 cycles. Rituximab should be administered on day 1 of each chemotherapy cycle, after intravenous (IV) administration of the glucocorticoid component of the chemotherapy if applicable. *Maintenance therapy*: • Previously untreated follicular lymphoma 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/m2 BSA 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 rituximab used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m2 BSA 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 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/m2 BSA, administered as an IV infusion once weekly for four weeks. 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/m2 BSA, administered as an IV infusion once weekly for four weeks.

	Adult Diffuse large B cell non-Hodgkin's lymphoma Rituximab should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after IV 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 rituximab are recommended. When rituximab is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied. *Chronic lymphocytic leukaemia* The recommended dosage of rituximab in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 BSA administered on day O of the first treatment cycle followed by 500 mg/m^2 BSA administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after rituximab infusion. **Paediatric population** <u>Non-Hodgkin's lymphoma</u> 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. The safety and efficacy of rituximab paediatric patients ~ 6 months to < 18 years of age has not been established in indications other than previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL. Only limited data are available for patients under 3 years of age. Rituximab should not be used in paediatric patients from birth to < 6 months of age with CD20 positive diffuse large B-cell lymphoma.

Part 2: Summary of Risk Management Plan

Important risks	Reasons or Evidence Indicating the aforementioned Risks	Pharmacovigilance Plan/Efficacy Study	Risk Minimization Plan
Important identified risks			
Infections, including serious infections (All Indications)	In alignment with the core RMP (EU RMP for Ituxredi v0.4 dated 03-July-2024)	**1. Routine Pharmacovigilance Activities:** • Adverse event monitoring • Monitoring of medical literature • Routine signal management review • Aggregate report submission **2. Additional Pharmacovigilance Activities:** None	**1. Routine Minimization Activities** Routine risk communication: • European Union (EU) Summary of Product Characteristics (SmPC) Section 4.4: Special warnings and precautions for use • Section 4.8: Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the Product Information: • *Medicine's legal status:* Medicinal product subject to restricted medical prescription **2. Additional risk minimization measures:** • Patient Alert Card (non- oncology indications) • Educational Material for Healthcare Professionals and Patients (non-

			oncology indications)
Progressive multifocal leukoencephalopathy (All Indications)	In alignment with the core RMP (EU RMP for Ituxredi v0.4 dated 03-July-2024)	**1. Routine Pharmacovigilance Activities:** • Adverse event monitoring • Specific adverse reaction FU questionnaire for the malignant events (non-oncology indications) and second malignancies [NHL/CLL]) • Specific adverse • reaction FU questionnaire for Progressive multifocal leukoencephalopathy (PML) • Monitoring of medical literature • Routine signal management review • Aggregate report submission **2. Additional Pharmacovigilance Activities:** None	**Routine risk minimization measures:** <u>Routine risk communication:</u> • EU SmPC Section 4.4: Special warnings and precautions for use • Section 4.8: Undesirable effects <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> "*Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. Further evaluations, includes Magnetic Resonance Imaging scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered. If a patient develops PML, the dosing of rituximab must be permanently discontinued*". <u>Other routine risk minimization measures beyond the Product Information:</u> • *Medicine's legal status*: Medicinal product subject to

			restricted medical prescription **2. Additional risk minimization measures**: • Patient Alert Card (non- oncology indications) Educational Material for Healthcare Professionals and Patients (non-oncology indications).
Hepatitis B reactivation (All indications)	In alignment with the core RMP (EU RMP for Ituxredi v0.4 dated 03-July-2024)	**1. Routine Pharmacovigilance Activities:** • Adverse event monitoring • Monitoring of medical literature • Routine signal management review • Aggregate report submission **2. Additional Pharmacovigilance Activities:** None	**1. Routine risk minimization measures**: <u>Routine risk communication</u>: • SmPC Section 4.4: Special warnings and precautions for use • Section 4.8: Undesirable effects <u>Routine risk minimization activities recommending specific clinical measures to address the risk</u>: • The Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with rituximab. At minimum this should include hepatitis B surface antigen (HBsAg)- status and hepatitis B core antibody (HBcAb)-status. These can be

			complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with rituximab. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. Other routine risk minimization measures beyond the Product Information: • *Medicine's legal status*: Medicinal product subject to restricted medical prescription **2. Additional risk minimization measures:** None
Hypogamma globulinaemia (Non-oncology indications)	In alignment with the core RMP (EU RMP for Ituxredi v0.4 dated 03-July-2024)	**1. Routine Pharmacovigilance Activities:** • Adverse event monitoring	**1. Routine risk minimization measures**: Routine risk communication:

		• Monitoring of medical literature • Routinebsignal management review • Aggregate report submission **2. Additional Pharmacovigilance Activities:** None	• EU SmPC Section 4.4: Special warnings and precautions for use • SmPC Section 4.8: Undesirable effects Routine risk minimization activities recommending specific clinical measures to address the risk: • Immunoglobulin levels are recommended to be determined prior to initiating treatment with rituximab. Other routine risk minimization measures beyond the Product Information: • *Medicine's legal status*: Medicinal product subject to restricted medical prescription **2. Additional risk minimization measures:** None
Important potential risks			
None	(EU RMP for Ituxredi v0.4 Dated 03-July-2024)	Not applicable	Not applicable
Missing information			
None	(EU RMP for Ituxredi v0.4 dated 03-July-2024)	Not applicable	Not applicable
Post-authorisation development plan: There are no studies which are conditions of the marketing authorisation or specific obligation of rituximab.			

Dr. Reddy's Laboratories (DRL) acknowledges that the healthcare settings and infrastructure may vary between countries, and following prequalification, DRL commits to evaluate the adequacy of the safety concerns with respect to the particular country. Additional safety concerns and risk related measures or activities if any will be added to the respective Risk Management Plan.

Dr. Reddy's will implement sufficient pharmacovigilance, risk minimization measures and product traceability following product prequalification even if differences, compared to SRAs, in healthcare settings and/or infrastructure are found at a national level.

Emerging Markets QPPV is responsible to establish contact with a PV focal person at the national PV centre or National Regulatory Authority (NRA) of the country for all safety issues. In case a focal PV point is not present at the National PV centre the processes and deliverables will be handled by Global PV team as per the DRL Global processes and the applicable SOPs.

WHO Prequalification of Medicines Programme supports procurement by agencies (WHO qualified) and Low middle income countries (LMIC).

Summary of the applicant's pharmacovigilance system

Dr Reddy´s Laboratories Ltd has Emerging Markets Qualified Person for Pharmacovigilance (EM QPPV) who resides in India and monitors PV activities.

At the time of submission, the contact details for the applicant's QPPV are:

Contact details:

Details of EM-QPPV & PVOIC:

Name:	Dr Chetan Karoo
Telephone:	+91 8019125817
Email:	chetankaroo@drreddys.com pharmacovigilance@drreddys.com
Office address (registered office):	Dr Reddy´s Laboratories Ltd, 8-2-337, Road No. 3, Banjara Hills, Hyderabad – 500034, Telangana, India

Details of Deputy EM-QPPV& PVOIC:

Name:	Pankaj Ramesh Khairnar
Telephone:	+91 9930600877
Email:	pankajrameshkhairnar@drreddys.com pharmacovigilance@drreddys.com
Office address (registered office):	Dr Reddy´s Laboratories Ltd, 8-2-337, Road No. 3, Banjara Hills, Hyderabad – 500034, Telangana, India

The applicant has a pharmacovigilance system at its disposal based on the legislation including:

- Adequate flow of safety reports, their collection, processing, quality control, coding, classification and medical review
- Screening of the local and global scientific literature
- Expedited reporting of Individual Case Safety Reports (ICSRs)
- Preparation and submission of Periodic Safety Update Reports

- Continuous monitoring of the safety profile of all authorised medicinal products
- RMP & Signal activites
- Use of an E2B compatible database software system
- Crisis management plan
- Training
- Documentation
- Pharmacovigilance Quality Management System.

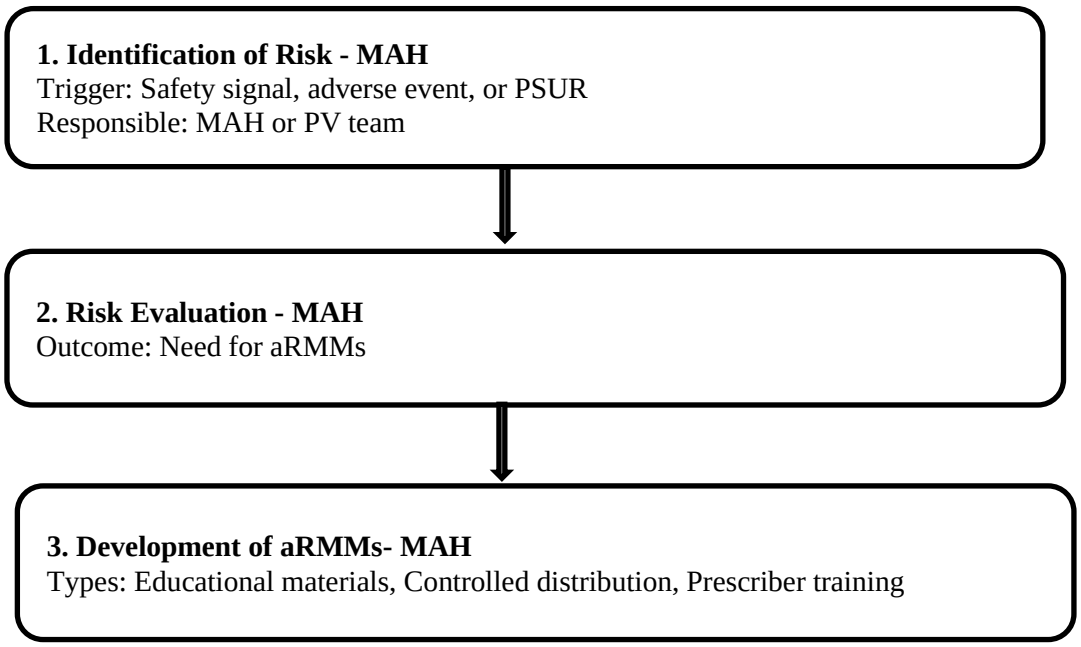
The applicant's Pharmacovigilance System Master File is located as below:
An electronic copy of the Core EM PSMF is available with EM QPPV (Emerging Markets QPPV) at Dr. Reddy's Laboratories Ltd. (registered office address as above, Hyderabad, India) and has access to a copy at all times.

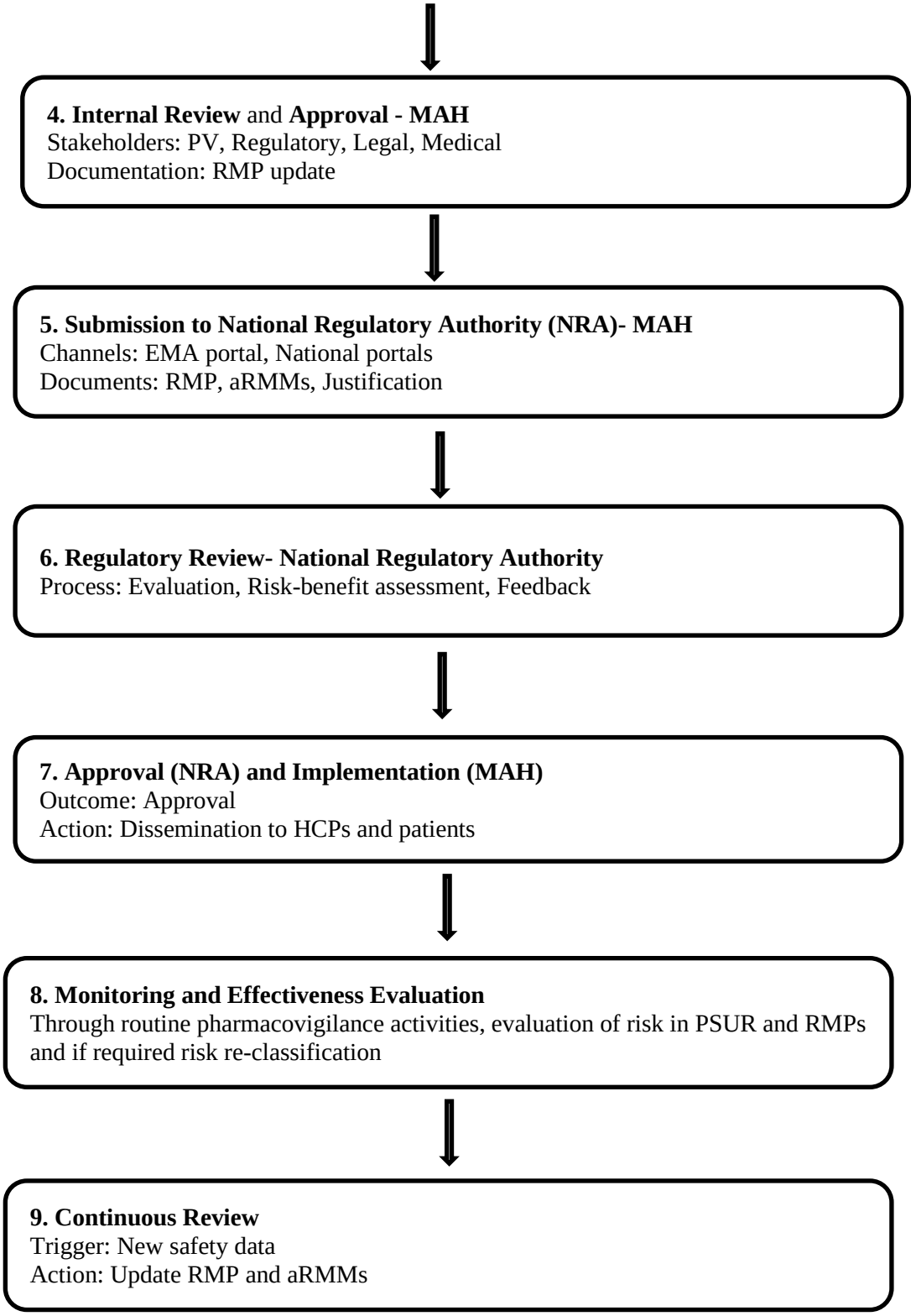
	Electronic copy of Core EM PSMF is available with EM QPPV located at below address
Location Details	Dr Reddy's Laboratories Ltd (DRL) 8-2-337, Road No. 3, Banjara Hills, Hyderabad – 500034 Telangana, India

The applicant's Pharmacovigilance System Master File number is **DRLCEM4.0**

Name	Dr Chetan Karoo
Job title/designation	Head PV India & Emerging Markets, EM-QPPV & PVOIC
Signature and Date	

Below is a flow chart/communication plan to share information with National Regulatory Authorities:





Dr Reddy's Regulatory affairs will share any RMP or a RMM related information via submission through national/portal channels or via e mail or as applicable with the respective NRA.

Dr. Reddy's Laboratories Ltd. (DRL) ensures that approval from National Regulatory Authority will be obtained for any and all risk minimisation measures, and will monitor that these are implemented and

are effective at National level.

Periodic Safety Update Reports (PSURs) as per SOP-GPV-GLOB-0023-Preparation and Submission of Aggregate Reports and Signal Detection based on periodic review of the safety data as per SOP-GPV-GLOB-0006 is done. As per the observations or findings during these processes, if required, we can establish additional PV activities (after approval from respective Health Authority) to target emerging safety issues or any other safety concerns. The local specificities considered for the assessment of a need for additional pharmacovigilance activities will cover epidemiology (e.g., infection), healthcare infrastructure, clinical practice, social, economic and other variables.

Periodic Safety Update Reports (PSURs) as per SOP-GPV-GLOB-0023 (Preparation and Submission of Aggregate Reports) will be prepared and submitted in accordance with the national requirements.

Dr. Reddy's Laboratories Ltd. (DRL) ensures that approval from National Regulatory Authority will be obtained for any and all risk minimisation measures. Additionally, we will adapt the aRMM according to the respective country specific clinical practice and the healthcare setting/infrastructure e.g. inclusion of checklist, etc. The implementation of aRMM measures will be done as per the WI-GPV-GLOB-0022 (Creation, approval & distribution of aRMM.

Rituximab is only used where there are adequate facilities to implement the RMMs. If close supervision by an experienced HCP is needed, eg for the risk of serious infections and PML, Rituximab will be given in an environment with facility to handle the associated adverse events (including close supervision by an experienced HCP in an environment with full resuscitation facilities are immediately available).

The implementation and effectiveness check of the additional risk minimisation measures will be done as per the WI-GPV-GLOB-0022 - Creation, approval & distribution of aRMM. DRL will ensure the approved aRMM implementation is completed as per the approved aRMM distribution plan by NRA and its effectiveness must be conducted and documented as per the country level procedure, if applicable.

Part 3: Traceability:

As part of logistics planning and dispatch process, pre-defined lanes are utilized for each destination, as listed in the master index (WI-BTO-SCM-0001, available at site). These lanes should be referred to by the logistics planner during dispatch booking.

Once booked, the assigned lanes are cross-checked against the master index and the House Airway Bill (HAWB) before being documented in the checklist for pick and pack export (FORM-BTO-WH-0075, available at site) by the warehouse team.

Shipping details shall be tracked using the HAWB provided by the logistics partner. Additionally, FORM-BTO-WH-0075 (available at site) includes multiple line clearance checkpoints. Details of the approved lane and the actual executed lane are documented. Upon successful dispatch to the destination, QA will finalize the checklist closure, including a review of data logger temperature readings.

GPS tracking enables and ensures real-time monitoring of domestic vehicle movement from the manufacturing plant to the airport. Airline tracking mechanism provides visibility to the shipment status as it moves between various ports. A datalogger is included in the shipment to continuously track temperature conditions from the plant to the consignee's door.

The tradename (Ituxiredi) and batch number of the administered product will be clearly recorded in the patient file.

Systems for Safeguarding Drug Product Distribution

Dr. Reddy's Laboratories Ltd. ensures secure pharmaceutical distribution through advanced serialization and traceability systems (Jekson) complying with regulatory standards to prevent counterfeiting and unauthorized distribution.

1. Serialization & Traceability
   - The Jekson ReeTrak system generates and tracks unique Serial Numbers for each product using SAP ATTP, ensuring complete product visibility.
   - Forward and backward tracking allows verification of product authenticity at any stage of distribution.
   - Scanning and challenge tests prevent duplicate, incorrect, or smudged barcodes, ensuring packaging accuracy.

2. Secure Supply Chain Control
   - SAP ATTP maintains a corporate serialization repository for compliance with international regulations.
   - Repacking procedures provide controlled replacement of damaged cartons to prevent unauthorized re-entry into the market.
   - Automated batch completion management ensures unused serial numbers are deactivated and sent back to ATTP, preventing misuse.

3. Compliance with Global Regulatory Standards
   - EU FMD Regulation (2016/161): Ensures product authentication before dispensing, preventing counterfeit entry into the market.
   - GS1 Standards: Guarantees globally recognized serialization protocols for tracking across supply chains.
   - 21 CFR Part 11 Compliance: Supports secure electronic records and 2D code verification.

By integrating serialization, authentication, and regulatory compliance, Dr. Reddy's Laboratories Ltd. safeguards drug distribution, ensuring patient safety and market integrity.