Summary of the Risk Management Plan (RMP) for HyQvia (Human Normal Immunoglobulin)

Marketing Autorisation Holder: Takeda Pharma AG
Version 4.0, 14.07.2022
Based on EU RMP version 13.1

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risk as well as to prevent or minimize them.

The RMP summary of HyQvia is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of HyQvia in Switzerland is the "Arzneimittelinformation / Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of HyQvia.

Summary of risk management plan for HyQvia (Human Normal Immunoglobulin)

This is a summary of the RMP for HyQvia. The RMP details important risks of HyQvia, and how more information will be obtained about HyQvia's risks and uncertainties (missing information).

HyQvia's SmPC and its PL give essential information to HCP and patients on how HyQvia should be used.

This summary of the RMP for HyQvia 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 HyQvia's RMP.

I. The medicine and what it is used for

HyQvia is authorised as replacement therapy in adults, children and adolescents (0-18 years):

- Primary immunodeficiency syndromes with impaired antibody production
- Secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l.

  *PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Kindly refer SmPC for the full indication. It contains human normal immunoglobulin as the active substance, and it is given by SC route.

Further information about the evaluation of HyQvia's benefits can be found in HyQvia's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/overview/hyqvia-epar-summary-public_en.pdf

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of HyQvia, together with measures to minimise such risks and the proposed studies for learning more about HyQvia'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 PL and SmPC addressed to patients and HCP;
- 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 addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of HyQvia is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of HyQvia 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 HyQvia. 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	Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency.
	Altered immune response: • Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella • Interference with serological testing after infusion of immunoglobulin.
	Infusion site reactions (infusion site leaking).
	Thromboembolic events (TEEs).
	Haemolysis/Haemolytic anaemia.
	Aseptic meningitis syndrome (AMS).
Important potential risks	Transmissible infectious agents.
	Spread of localised infection.
	Renal dysfunction/failure.
	Drug administration error: incorrect sequence of administration of products.
Missing information	Limited information on safety in pregnant and lactating women.

	Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years.
	Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20.

II.B Summary of important risks

Important Identified Risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	
Evidence for linking the risk to the medicine	Medical literature, potential mechanism of action.
Risk factors and risk groups	The IG 10% component of HyQvia contains trace amounts of IgA. Patients with antibodies to IgA potentially have a greater risk of developing severe hypersensitivity or anaphylactic reactions. One article state that SC immunoglobulin therapy is associated with a less than 1% risk of systemic reactions during infusion. A study of immediate hypersensitivity reactions in 100 healthy volunteers, injected intradermally with 0.1 ml of rHuPH20 solution (150 U/ml), showed absence of reaction in all subjects (Halozyme Study R04-0851).
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.3 SmPC Section 4.4 and PL section 4 where advice given to train the patients to detect early signs of hypersensitivity reactions and monitored the patients throughout the infusion period. SmPC Section 4.8 PL Section 2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

Important Identified Risk: **Altered immune response:** • **Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella** • **Interference with serological testing after infusion of immunoglobulin**	
Evidence for linking the risk to the medicine	Medical literature
Risk factors and risk groups	All patients who receive immunoglobulin therapy are potentially at risk for altered immune responses.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.4 and PL section 2 where advice is given wait for up to 3 months before receiving certain vaccines and inform the doctor about the treatment with HyQvia before any blood test. SmPC Section 4.5 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

Important Identified Risk: Infusion site reactions (infusion site leaking)	
Evidence for linking the risk to the medicine	Medical literature, clinical trials, potential mechanism of action
Risk factors and risk groups	Local reactions are a known risk of any SC infusion.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 PL Section 2 PL Section 4 SmPC Section 4.4 and PL section 3 contains advice to use longer needles and/or more than one infusion site to avoid infusion site leakage. **Additional risk minimisation measures:** None.

Additional pharmacovigilance activities	None

Important Identified Risk: Thromboembolic events (TEEs)	
Evidence for linking the risk to the medicine	SmPC, CCSI, medical literature, post-marketing reports
Risk factors and risk groups	Patients at increased risk for thrombotic events include those with: • A history of atherosclerosis. • Multiple cardiovascular risk factors. • Advanced age. • Impaired cardiac output. • Hypercoagulable disorders. • Prolonged periods of immobilisation. • Obesity. • Diabetes mellitus. • Acquired or inherited thrombophilic disorder. • A history of vascular disease. • A history of a previous thrombotic or TEE.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.4 where advice is given to monitor the patient for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity and patients should be sufficiently hydrated before use of immunoglobulins. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

Important Identified Risk: Haemolysis/Haemolytic anaemia	
Evidence for linking the risk to the medicine	SmPC, CCSI, medical literature, post-marketing reports
Risk factors and risk groups	Patients with blood groups A, B, or AB receiving immune globulin therapy are potentially at risk.

Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.4 advice to monitor the patients for clinical signs and symptoms of haemolysis. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

Important Identified Risk: Aseptic meningitis syndrome (AMS)	
Evidence for linking the risk to the medicine	SmPC, CCSI, medical literature, post-marketing reports
Risk factors and risk groups	Aseptic meningitis syndrome has been reported to occur in association with IV and SC immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high-dose (2 g/kg) IV immunoglobulin treatment. From post-marketing data no clear correlation of AMS to higher doses was observed. Higher incidences of AMS were seen in women.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.4 mention that AMS symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about first symptoms AMS. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.

Additional pharmacovigilance activities	None

Important potential risks: Transmissible infectious agents	
Evidence for linking the risk to the medicine	Medical literature
Risk factors and risk groups	Any patient who is administered a blood- or plasma-derived medicinal product is potentially at risk for transmission of infectious agents.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.4 contains the standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

Important potential risks: Spread of localised infection	
Evidence for linking the risk to the medicine	Medical literature
Risk factors and risk groups	Patients with existing localised infections or acute inflammation who receive SC infusion are at risk for the spread of localised infection.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.2 PL Section 2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

Important potential risks: Renal dysfunction/failure	
Evidence for linking the risk to the medicine	SmPC, CCSI, medical literature, post-marketing reports
Risk factors and risk groups	Cases of acute renal failure have been reported in patients receiving IV administered immunoglobulins, and in most cases, other risk factors have been identified, such as preexisting renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant use of nephrotoxic medicinal products, or age over 65 years.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

Important potential risks: Drug administration error: incorrect sequence of administration of products	
Evidence for linking the risk to the medicine	Theoretical risk
Risk factors and risk groups	All patients who receive HyQvia therapy are potentially at risk for medication error. However, patients who participate in home administration are at greater risk compared to those who receive therapy under the supervision of an HCP.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 2 SmPC Section 4.2 contains the recommended infusion rate. SmPC Section 4.4 where advice is given on monitoring and management of adverse reaction. PL Section 3 PL Section 6 **Additional risk minimisation measures:**

	Educational materials proposed
Additional pharmacovigilance activities	None

Missing Information: Limited information on safety in pregnant and lactating women	
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.6 and PL Section 2 where fertility, pregnancy and lactation are discussed **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Missing Information: Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years	
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.6 SmPC Section 4.8 SmPC Section 5.1 SmPC Section 5.2 PL Section 2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	Study 161503 (Category 3)

Missing Information: Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	Study 161302 (Category 1) Study 161406 (Category 3) Study 161503 (Category 3) Study 161504 (Category 3)

II.C Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the MA

No studies are conditions of the marketing authorisation.

II.C.2. Other Studies in Postauthorization Development Plan

Study 161406

Purpose of the study:

To evaluate safety data in patients with PID This study is a post market commitment to the FDA. (US only).

Study 161503

Purpose of the study:

To evaluate safety of HyQvia treatment in paediatric subjects with PIDD who have received prior IV or SC immunoglobulin therapy before enrollment into the study.

Further safety assessments (e.g., immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, efficacy (immunoglobulin G trough levels), and PK parameters.