EMA/622537/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

Type II group of variations assessment report

Procedure No. EMEA/H/C/002491/II/0070/G

Invented name: HyQvia

International non-proprietary name: human normal immunoglobulin

Marketing authorisation holder (MAH): Baxalta Innovations GmbH

This application is in the area of: (Non-)Clinical RMP

eCTD sequences related to the procedure: 0145

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Baxalta Innovations GmbH submitted to the European Medicines Agency on 30 March 2021 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

C.I.4 - Update of section 4.6 of the SmPC in order to update information on pregnancy and breast-feeding based on the final results from Study 161301 listed as a category 3 study in the RMP; this is an observational study to collect long-term safety data from women treated with HyQvia.
The package leaflet has been updated accordingly. RMP version 12.0 has also been submitted.
In addition, the MAH took the opportunity to implement minor corrections and editorial changes to the SmPC.

C.I.11.b – Submission of an updated RMP version 12.0 to update the educational material section Part V.2, additional Risk Minimisation Measures, for HyQvia. The change was agreed by the PRAC in the outcome of the PSUSA procedure EMEA/H/C/PSUSA/00001633/202005.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

Immune Globulin Infusion 10% (IGI 10%) with recombinant human hyaluronidase (rHuPH20) is a product combination (HyQvia) for facilitated subcutaneous administration of the IGI 10% for replacement therapy in primary and secondary immunodeficiencies. The medicinal product is provided as two components in a dual vial unit in an inseparable kit arrangement. Medication errors, including confusion of the administration order of the components, is considered an important potential risk. An increase in medication error reports triggered the introduction of educational material as additional risk minimization measure.

The pregnancy registry study 161301 was a commitment to the Committee for Medicinal Products for Human Use (CHMP) and the FDA, and aimed to address safety concerns in women who become pregnant during or after treatment with HyQvia (including assessment of anti-rHuPH20 antibodies), as well as the physical and neurological development of the infant during the first 2 years of life.

Study 161301 was a non-interventional, uncontrolled, two-arm, open-label, multicentre post-authorization pregnancy registry of women treated with HyQvia and open for enrollment for 3.5 years. The study had 2 arms based on whether or not HyQvia treatment was continued during pregnancy and patients were also included retrospectively.

A total of 9 mothers were enrolled, 7 were included in the retrospective cohort, of which 5 completed follow up, and 2 were included in the prospective cohort, and completed follow up. Data on HyQvia treatment was available for 6 (85.7%) mothers in the HyQvia Arm (4 mothers in the retrospective cohort and 2 mothers in the prospective cohort). These patients received a total of 26 infusions. Adverse events reported in HyQvia Arm of the registry were not consistent with the most common adverse reactions observed in clinical trials with HyQvia. A total of 2 SAEs were reported in 1 (11.1%) mother who was in HyQvia Arm and from the Prospective cohort (PT: thrombocytopenia; pre-eclampsia). None of the SAEs were assessed as related to HyQvia treatment. None of the (non-serious) AEs reported in the study were assessed as related to previous or current HyQvia treatment in the mother, or caused HyQvia treatment changes.

Four mothers were tested for anti-rHuPH20 binding or neutralizing antibodies (2 in the HyQvia Arm, 2 Alternative Product Arm) and no antibodies were detected but the significance of this finding is limited. Data accuracy and presentation could have been improved in the study report and Clinical Overview Addendum.

Five mothers continued HyQvia treatment during the pregnancy (2 mothers enrolled before delivery and 3 mothers enrolled after delivery with ongoing HyQvia treatment at the screening visit) and all had live births, with normal APGAR scores. By the end of the study, a total of 7 infants were included in the Enrolled set, of which 5 were included in the Retrospective cohort and 2 in the Prospective cohort. Two out of 5 (40.0%) infants (all in HyQvia Arm) had presence of congenital malformations/ anomaly that were assessed as mild in severity (Cleft lip, Talipes) and were assessed as not related to their mother's previous and current HyQvia treatment. Data on infant follow up was incomplete, highly fragmented, inaccurately described and the data presentation in the study report could have been greatly improved.

Overall, the study report’s conclusion appears overstated in view of the very small sample size and fragmented data but no new significant safety concerns emerged. Due to the still limited information on safety in pregnant and lactating women, any cases of drug exposure during pregnancy should be follow-up and presented in PSURs as cases of special interest. Participation in registries that aim to assess outcome of drug exposure during pregnancy (cf. EUROCAT network) could be encouraged in such cases.

The benefit-risk balance of HyQvia remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.11.b	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	Type II	None
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

C.I.4 - Update of section 4.6 of the SmPC in order to update information on pregnancy and breast-feeding based on the final results from Study 161301 listed as a category 3 study in the RMP; this is an observational study to collect long-term safety data from women treated with HyQvia.
The package leaflet has been updated accordingly. RMP version 12.0 has also been submitted.
In addition, the MAH took the opportunity to implement minor corrections and editorial changes to the SmPC.

C.I.11.b – Submission of an updated RMP version 12.0 to update the educational material section Part V.2, additional Risk Minimisation Measures, for HyQvia. The change was agreed by the PRAC in the outcome of the PSUSA procedure EMEA/H/C/PSUSA/00001633/202005.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

In view of the very limited data from the result of a non-interventional, prospective, uncontrolled, two-arm, open-label, multicentre post-authorisation pregnancy registry of women treated with HyQvia, section 4.6 of the SmPC has been updated to state that from a total of nine women enrolled in this study, and of the eight pregnancies with known outcomes, there were eight live births with normal APGAR scores. There were no specified labor or delivery complications. Four mothers were tested for anti-rHuPH20 binding or neutralizing antibodies and no antibodies were detected.

Subsection Breast-feeding of section 4.6 has been updated to add that one infant in the study was breastfed and that all adverse events were reported as not related to previous or current HyQvia treatment.

Section B point 2 of the Package Leaflet is updated accordingly and several editorial changes that do not change the content of the previously approved SmPC are introduced in sections 3, 4.2, 4.4 and 4.7.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Immune Globulin Infusion 10% (IGI 10%) with recombinant human hyaluronidase (rHuPH20) is a product combination (HyQvia) for facilitated subcutaneous administration of the IGI 10%. HyQvia is intended for use in adults, children and adolescents (0-18 years) for replacement therapy in primary immunodeficiency syndromes (PID) and in secondary immunodeficiencies (SID) 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.

The medicinal product is provided as two components in a dual vial unit in an inseparable kit arrangement. Recombinant human hyaluronidase (rHuPH20), classified as an excipient, is a solution for subcutaneous injection that functions as a permeation enhancer. The two components are administered sequentially through the same needle beginning with the recombinant human hyaluronidase followed by IGI 10%. Medication errors, including confusion of the administration order of the components, is considered an important potential risk.

The pregnancy registry study 161301 was a commitment to the Committee for Medicinal Products for Human Use (CHMP) and the FDA, and aimed to address safety concerns in women who become pregnant during or after treatment with HyQvia (including assessment of anti-rHuPH20 antibodies), as well as the physical and neurological development of the infant during the first 2 years of life.

6. Clinical Safety aspects

6.1. Topic 1 - study 161301 (Pregnancy Registry)

6.1.1. Methods – analysis of data submitted

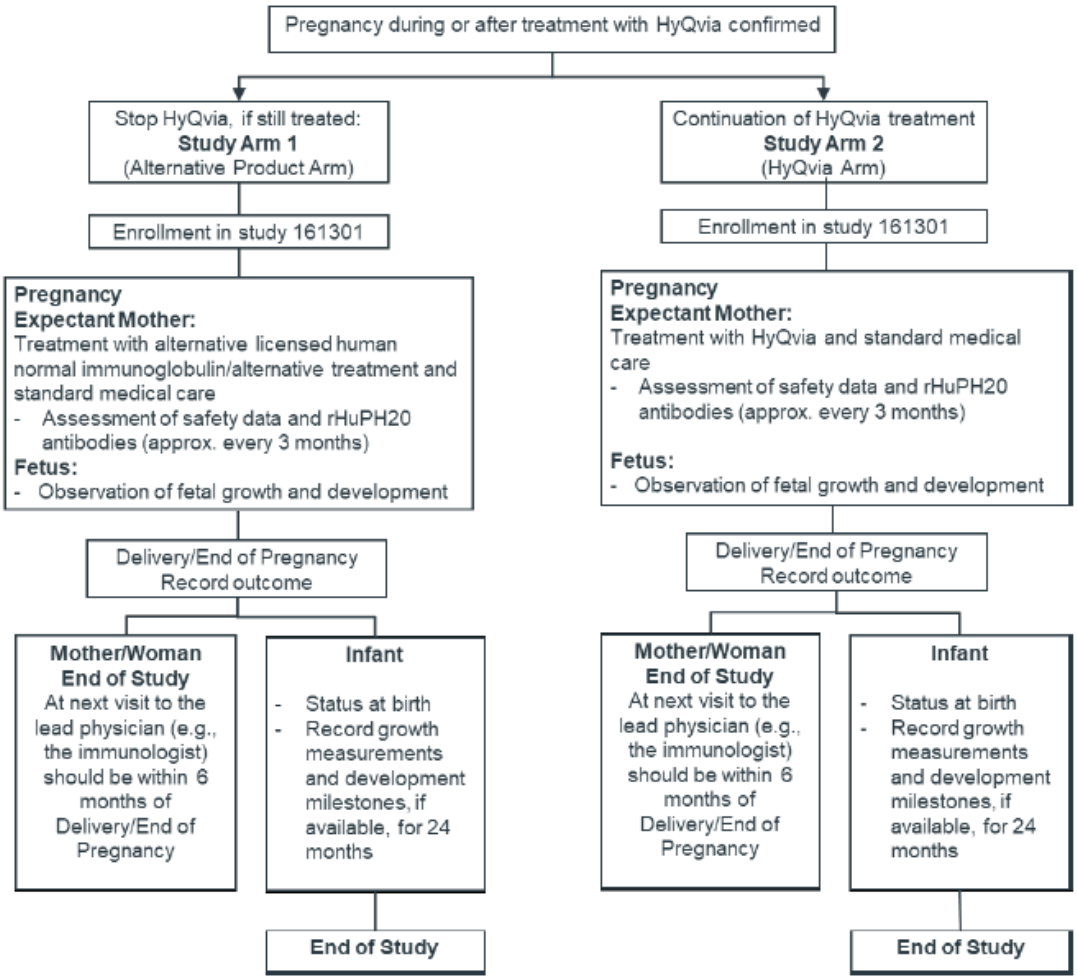
Study 161301 was a non-interventional, prospective, uncontrolled, two-arm, open-label, multicentre post-authorization pregnancy registry of women treated with HyQvia. The study was conducted at 8 sites across US (n=1), Czech Republic (n=1), Germany (n=3), Poland (n=1), and Slovakia (n=2). The enrollment was open for approximately 3.5 years. There was no pre-specified minimum sample size for this registry.

The study had 2 arms based on whether or not HyQvia treatment was continued during pregnancy.

- Study Arm 1 (Alternative Product Arm): subjects who stopped HyQvia treatment (if the subjects were still treated) and a licensed human normal immunoglobulin other than HyQvia for IV or SC infusion or an alternative treatment were administered, as determined by the treating physician. Subjects in countries where HyQvia treatment during pregnancy was not indicated were enrolled in Study Arm 1. The date and gestational age were collected for any subject in the Alternative Product Arm who restarted HyQvia.
- Study Arm 2 (HyQvia Arm): subjects who continued to receive HyQvia according to their treatment regimen.

Patients could also been included retrospectively.

Figure 1. Study Flow Chart



Primary Endpoint

The primary endpoint was the incidence of all serious adverse events (SAEs) in expectant mothers and infants.

Secondary Endpoints

• Incidence of non-serious AEs, related and not related to HyQvia/human normal IG or alternative treatment (expectant mothers and infants)
• Incidence of local/immunologic AEs, including skin changes (such as: local erythema, local pruritus, induration, nodules) (expectant mothers)
• Development of antibodies against rHuPH20 (rHuPH20 binding and neutralizing antibodies) (expectant mothers)
• Complications of pregnancy
• Fetal growth/development
• Outcome of pregnancy
• Neonatal assessment
• Status of the infant at birth
• Growth measurement and charts for the infant, if available
• Development milestones determined by standard test methods, for each region, if available

6.1.2. Results

A total of **9 mothers** were screened for the study and enrolled. Seven (7) mothers were included in the retrospective cohort, of which 5 (77.8%) completed follow up, and 2 mothers were included in the prospective cohort, of which all completed follow up.

Data on the actual HyQvia treatment was available for 6 (85.7%) mothers in the HyQvia Arm (4 mothers in the retrospective cohort and 2 mothers in the prospective cohort). These patients received a total of 26 infusions, with 96.2% of infusions being administered at home.

From the 9 mothers, 2 of their infants were not enrolled in the study because one mother withdrew consent prior to delivery and the pregnancy outcome is unknown and the other mother was lost to follow-up after delivery and did not consent her infant to be included in the study. By the end of the study, a total of **7 infants** were included in the Enrolled set, of which 5 were included in the Retrospective cohort and 2 in the Prospective cohort.

Adverse events reported in HyQvia Arm of the registry were not consistent with the most common adverse reactions observed in clinical trials with HyQvia. A total of 2 SAEs were reported in 1 (11.1%) mother who was in HyQvia Arm and from the Prospective cohort, including blood and lymphatic system disorders (PT: thrombocytopenia; n=1, 14.3%) and pregnancy, puerperium and perinatal conditions (PT: pre-eclampsia; n=1, 14.3%). None of the SAEs were assessed as related to HyQvia treatment. None of the (non-serious) AEs reported in the study were assessed as related to previous or current HyQvia treatment in the mother, or caused HyQvia treatment changes (i.e., dose reduction, interruption, withdrawal). No anti-rHuPH20 binding or neutralizing antibodies (four mothers tested), or local and immunologic AEs were reported in this registry that were assessed as related. Five mothers continued HyQvia treatment during the pregnancy (2 mothers enrolled before delivery and 3 mothers enrolled after delivery with ongoing HyQvia treatment at the screening visit) and all had live births, with normal APGAR scores.

Table 13. Mother: Adverse Events by System Organ Class and Preferred Term (Enrolled Set)

Cohort	System Organ Class Preferred Term	Alternative Product Arm		HyQvia Arm		Total	
		Number of Patients (N=2)	Number of Events	Number of Patients (N=7)	Number of Events	Number of Patients (N=9)	Number of Events
Overall	Any AE, n(%)	1 (50.0)	5	3 (42.9)	8	4 (44.4)	13
	Blood and lymphatic system disorders	0 (0.0)	0	2 (28.6)	3	2 (22.2)	3
	Anaemia of pregnancy	0 (0.0)	0	2 (28.6)	2	2 (22.2)	2
	Thrombocytopenia	0 (0.0)	0	1 (14.3)	1	1 (11.1)	1
	Infections and infestations	1 (50.0)	3	1 (14.3)	2	2 (22.2)	5
	Bronchitis	1 (50.0)	1	0 (0.0)	0	1 (11.1)	1
	Genital herpes simplex	1 (50.0)	1	0 (0.0)	0	1 (11.1)	1
	Influenza	0 (0.0)	0	1 (14.3)	1	1 (11.1)	1
	Laryngitis	1 (50.0)	1	0 (0.0)	0	1 (11.1)	1
	Urinary tract infection	0 (0.0)	0	1 (14.3)	1	1 (11.1)	1
	Investigations	1 (50.0)	1	0 (0.0)	0	1 (11.1)	1
	Hepatic enzyme increased	1 (50.0)	1	0 (0.0)	0	1 (11.1)	1
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (50.0)	1	0 (0.0)	0	1 (11.1)	1
	Anogenital warts	1 (50.0)	1	0 (0.0)	0	1 (11.1)	1
	Pregnancy, puerperium and perinatal conditions	0 (0.0)	0	1 (14.3)	3	1 (11.1)	3
	Pre-eclampsia	0 (0.0)	0	1 (14.3)	2	1 (11.1)	2
	Uterine contractions during pregnancy	0 (0.0)	0	1 (14.3)	1	1 (11.1)	1

Two out of 5 (40.0%) infants (all in HyQvia Arm) had presence of congenital malformations/anomaly that were assessed as mild in severity (Cleft lip, Talipes) and were assessed as not related to their mother's previous and current HyQvia treatment.

At approximately 6-month follow-up, no congenital malformations diagnosed that were not reported at birth or conditions that were noted since birth were reported (data available for 2 out of 7 infants). Of the infants with weight information (n=3, 42.9%), all had normal weight. Length and head circumference information was available in 2 (28.6%) infants, of these, all infants had normal length and head circumference. Information on breastfeeding at the 6-month follow-up was available for one infant.

At approximately 12-month follow-up, weight, length and head circumference information was available in 2 (28.6%) infants, all with normal measurements. Information on breastfeeding at the time of the 12-months follow-up was available for 1 (14.3%) infant, who was breastfed, but breastfeeding duration was not available.

At approximately 18-months follow-up, weight, length and head circumference information was available in 1 (14.3%) infant, with normal measurements. Information on developmental milestones were available in 1 (14.3%) infant who had no evidence of missed developmental milestones.

At approximately 24-months follow-up, weight, length and head circumference information was available in 1 (14.3%) infant who had normal measurements. Two (28.6%) infants had available information on developmental milestones with one of them reporting to have missed milestones at the 24-month follow-up. The infant that reported having missed milestones, did reach 'sat up without support', 'turned to locate voice', and 'stand without support/help' milestones, and had unknown information on the milestones of rolled over, attend to and reached object, and said first words.

6.1.3. Discussion

In view of the very small sample size and fragmented data, in particular for the infants, the study report's conclusion appears overstated. Data presentation could be greatly improved. According to the MAH the small sample size of the registry study is related to the restricted pregnancy wording in the US and EEA product information.

The report often states that no unexpected measurements or events were reported but it is not clear whether this information was actually available for all individuals or just individual subjects. For example, at 6-month follow-up of infants, it is stated that no congenital malformations diagnosed that were not reported at birth or conditions that were noted since birth were reported, which sounds positive. However, according to the listings in the annex, it appears that this data was only available for 2 out of 7 infants in which case the initial statement is misleading. While the MAH states that at the 12-month follow-up, all available weight and length measurements were normal, it appears from the listing in the annex that measurements were rather unusual for one child (on day 365: length 57 cm, weight 6.27 kg, head circumference 38.7 cm), which should be discussed in more detail even though the mother was in the alternative product arm.

With respect to the mothers, anti-rHuPH20 antibody assessments were intended to be performed every 3 months. However, the two mothers in the HyQvia arm were tested only once. In total four mothers were tested and no antibodies were detected but the significance of this finding is limited.

It is positive to note that 7 mothers gave birth to live and healthy children. The statement that the growth and development of infants were followed for up to 2 years post-delivery appears to be true for one (1) child; even six months after birth data was available for less than half of the enrolled infants and only for some parameters. Therefore, no conclusions can be drawn on the physical and neurological development of infants during the first 2 years if mothers were exposed to HyQvia during pregnancy.

Any cases of drug exposure during pregnancy should be follow-up and presented in future PSURs as cases of special interest. In such cases, participation in registries that aim to assess outcome of drug exposure during pregnancy (cf. EUROCAT network) could also be encouraged.

In summary, the limited sample size of the pregnancy registry precludes any scientific robust conclusion. The proposed revision of section 4.6 of the SmPC therefore needs to be revised substantially.

6.2. Topic 2 - Additional Risk Minimisation Measures: Educational Material

6.2.1. Methods – analysis of data submitted

No new data was submitted. In the last PSUR (EMEA/H/C/PSUSA/00001633/202005), a high reporting rate for medication errors was noticed. In a considerable fraction of cases, confusion of the order of administration of rHuPH20 and Ig 10% appeared to be the problem. Thus, the MAH was requested to address this issue and to propose educational materials as additional risk minimization measure in the RMP (cf. section Risk management plan below).

6.2.2. Results

cf. section Risk management plan below

6.2.3. Discussion

cf. section Risk management plan below

7. Risk management plan

The MAH submitted an updated RMP version 12.0 with this application. The proposed RMP changes were the following:

Missing information language for 'Lack of information on safety in pregnant and lactating women' is updated to 'Limited information on safety in pregnant and lactating women' throughout the RMP.

Pharmacovigilance plan

Updated the status of Study 161301.

Additional Risk Minimisation Measures

Educational materials proposed to aid prescribers/users in ensuring they are well informed about the correct sequence of administration of HyQvia and its excipients.

Annexes:

Updated the status of Study 161301 under Annex 2 and Annex 3.

Updated information about proposed educational materials under Annex 6.

RMP Module:	Significant Changes:
Part I Product Overview	Not applicable.
Part II Safety Specification	
Module SI Epidemiology of the indication(s) and target population(s)	Not applicable.
Module SII Non-clinical part of the safety specification	Not applicable.
Module SIII Clinical trial exposure	Not applicable.
Module SIV Populations not studied in clinical trials	Information added on the number of patients included in study 161301 (Pregnancy Registry). *PRAC assessor comment: update agreed*
Module SV Post-authorisation experience	Updated information on patient exposure based on most recent sales data. *PRAC assessor comment: update agreed*
Module SVI Additional European Union (EU) requirements for the safety specification	Not applicable.
Module SVII Identified and potential risks	Missing information language for 'Lack of information on safety in pregnant and lactating women' is updated to 'Limited information on safety in pregnant and lactating women'. No new safety concerns identified. *Consult detailed PRAC assessor comment below.*
Module SVIII Summary of the safety concerns	Missing information language for 'Lack of information on safety in pregnant and lactating women' is updated to 'Limited information on safety in pregnant and lactating women' *PRAC assessor comment: update agreed*
Part III Pharmacovigilance plan	Updated the status of Study 161301. *Consult detailed PRAC assessor comment below.*
Part IV Plans for post-authorisation efficacy studies	Not applicable.
Part V Risk minimisation measures	Updated to be consistent with Module SVII and Module SVIII for Missing information Additional Risk Minimisation Measures Educational materials proposed to aid prescribers/users in ensuring they are well informed about the correct sequence of administration of HyQvia and its excipients. *Consult detailed PRAC assessor comment below*
Part VI Summary of the risk management plan	Updated to be consistent with Module SVII and Module SVIII for Missing information
Part VII Annexes	Updated the status of Study 161301 under Annex 2 and Annex 3. Updated information about proposed educational materials under Annex 6.

	Consult detailed PRAC assessor comment below

Summary of safety concerns

Summary of safety concerns	
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.

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	**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 monitor the patients throughout	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	the infusion period. SmPC Section 4.8 PL Section 2 **Additional risk minimisation measures:** None.	None
Important identified risks: 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	**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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important identified risks: Infusion site reactions (infusion site leaking)	**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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Leakage or site leaking questionnaire. **Additional pharmacovigilance activities:** None.
Important identified risks: Thromboembolic events (TEEs)	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Expedited reporting of all TEEs. TEE questionnaire.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	hydrated before use of immunoglobulins. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.	**Additional pharmacovigilance activities:** None.
Important identified risks: Haemolysis/Haemolytic anaemia	**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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important identified risks: Aseptic meningitis syndrome (AMS)	**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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risks: Transmissible infectious agents	**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**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures: None.	None.
Important potential risks: Spread of localised infection	**Routine risk minimisation measures:** SmPC Section 4.2 PL Section 2 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risks: Renal dysfunction/failure	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risks: Drug administration error - incorrect sequence of administration of products	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information: Limited information on safety in pregnant and lactating women	**Routine risk minimisation measures:** SmPC Section 4.6 and PL Section 2 where fertility, pregnancy and lactation are discussed **Additional risk minimisation**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures: None.	**activities:** Study 161301 (Category 3).
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	**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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Study 161503 (Category 3) Study 161504 (Category 3).
Missing information: Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Study 161302 (Category 1) Study 161406 (Category 3) Study 161503 (Category 3) Study 161504 (Category 3)

PRAC assessor comment:

The MAH submitted an updated RMP version 12.0 to address two aspects:

- *updates as a result of the recently completed study 161301 (Pregnancy Registry),*
- *include educational material as additional Risk Minimisation Measures to address an increasing number of medication error reports.*

While most changes could be acceptable in general, minor revisions are requested (RSI).

Study 161301

In Module SVII, the MAH updated the missing information 'Lack of information on safety in pregnant and lactating women' was updated to 'Limited information on safety in pregnant and lactating women' due to the completion of study 161301. The statement that "No clinical studies have been done in women who are pregnant or breast-feeding" was removed by the MAH. While the limited data available does not suggest a different safety profile, the study enrolled so few participants that no reliable conclusions can be drawn and this should be stated accordingly in this section. The number of women included and the fraction tested for anti-rHuPH20 antibodies should be clearly stated.

Information on the status of study 161301 was updated; the status was changed to "completed" in the pharmacovigilance plan (part III). However, the pharmacovigilance plan lists ongoing and planned pharmacovigilance activities and since study 161301 was completed, it should not be included in this part of the RMP any longer.

In annex 2, the subsection "Safety concerns addressed" for study 161301 was changed from "Lack of information on safety in pregnant and lactating women" to "Limited information on safety in pregnant and lactating women. However, limited information has only been available since study completion and the aim of the study was to address the lack of information (…). Thus, this change is not acceptable and should be undone.

<u>Educational material</u>
In the last PSUR (EMEA/H/C/PSUSA/00001633/202005), a high reporting rate for medication errors was noticed. In a considerable fraction of cases, confusion of the order of administration of rHuPH20 and Ig 10% appeared to be the problem. Thus, the MAH was requested to address this issue and included educational materials as additional risk minimization measure in RMP part V.
However, the anticipated target audience(s) is not exactly clear in the currently proposed version. The MAH writes: "The target audience is the healthcare providers who prescribe HyQvia. The MAH proposes this educational material will be available to users." Usually, education materials directed towards HCP and patients tend to differ. In this particular case, medication error reports necessitate the implementation of educational material to highlight the correct sequence of administration of HyQvia to patients using it. In addition, HCPs prescribing the product should be made aware of the risk of medication errors and the importance to ensure that their patients understand the correct sequence of the HyQvia administration. Thus, HCP-directed education material could support HCPs in training patients. Moreover, material for patients may help to remember the correct sequence and technique. The mentioned website with video material supplemented by leaflets may be suitable although the RMP should be revised to make the objectives, target audiences and intended content clearer.

With regard to the proposed effectiveness evaluation, a detailed review of related reports in the next PSUR appears reasonable. Since medication errors represent a potential risk of HyQvia, post-marketing data in this respect will be evaluated carefully in general.
RMP annex 6 was updated to include Details of Proposed Additional Risk Minimization Measures, which read as the outline included in part V.2 and contains no additional information. The above comments should be considered and in addition it should be expanded to include the statement that prescribes will be made aware of the risk of medication errors if the correct sequence of the HyQvia administration is not understood.

Existing guidelines for educational materials (cf. EMA/204715/2012 Rev 2, EMA/61341/2015) should be taken into consideration. National requirements regarding the training of patients for self-administration of parenteral medications may be applicable. HCP and patient educational materials may require to be submitted to national regulatory agencies for approval prior to launch.

The MAH has updated the RMP (version 12.1) accordingly to reflect the suggestion made by the PRAC.

7.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

8. Changes to the Product Information

As a result of this group of variations, section 4.6 of the SmPC is being updated. The Package Leaflet (PL) is updated accordingly (Section B. Package Leaflet, Point 2). In addition, a series of editorial changes that do not change the content of the previously approved SmPC are introduced in sections 3, 4.2, 4.4 and 4.7.

In view of the very small sample size and fragmentary data, the study report conclusion and the proposed changes in the SmPC appear overstated. The statement that the growth and development of infants were followed for up to 2 years post-delivery is true for one (1) child; even six months after birth data was available for less than half of the enrolled infants and only for some parameters. Similarly, the statement that no anti-rHuPH20 binding or neutralizing antibodies had developed should include the information that only four (4) women were tested for the presence of such antibodies.

Please refer to Attachment 1, which includes the requested modifications for section 4.6.

9. Request for supplementary information

9.1. Major objections

Clinical aspects

RMP aspects

9.2. Other concerns

Clinical aspects

1. The growth of one infant is rather unusual at 12-months and no later follow-up data appears to be available. The MAH is asked to summarize all information available on this child, time points of product exposure in the mother, and justify that the measurements were stated as normal.
2. The MAH is encouraged to investigate participation in registries that aim to assess outcome of drug exposure during pregnancy (cf. EUROCAT network). The MAH is kindly asked to comment upon.

RMP aspects

3. The MAH is asked to submit an updated RMP addressing the following issues:

a. *I*n Module SVII, it should be stated that while the limited data available does not suggest a different safety profile, study 161301 enrolled so few participants that no reliable conclusions can be drawn.

b. The number of women included in the study and the fraction tested for anti-rHuPH20 antibodies should be clearly stated.

c. The pharmacovigilance plan (RMP part III) lists ongoing and planned pharmacovigilance activities and since study 161301 was completed, it should not be included in this part of the RMP any longer.

d. In annex 2, the change in the subsection "Safety concerns addressed" for study 161301 was updated but should represent the original concern addressed at the start of the study and should be undone.

4. The information on educational material as additional risk minimisation measure should be revised to make the objectives, target audiences and intended content clearer (RMP part V.2 and annex 6). HCPs prescribing the product need to be made aware of the risk of medication errors and the importance to ensure that their patients understand the correct sequence of the HyQvia administration and HCP-directed education material could support HCPs in training patients. Moreover, material for patients may help to remember the correct sequence and technique. Please submit an updated RMP.

SmPC aspects

5. In summary, the limited sample size of the pregnancy registry precludes any scientific robust conclusion. The proposed revision of section 4.6 of the SmPC therefore needs to be revised substantially.

10. Assessment of the responses to the request for supplementary information

10.1. Major objections

Clinical aspects

RMP aspects

10.2. Other concerns

Clinical aspects

Question 1 The growth of one infant is rather unusual at 12-months and no later follow-up data appears to be available. The MAH is asked to summarize all information available on this child, time points of product exposure in the mother, and justify that the measurements were stated as normal.

Summary of the MAH's response
One infant's birthdate was partial in one data field and full in another which caused the extreme growth percentile calculation. We updated the SDTM (Study Data Tabulation Model) to use the full date from the different date field and reprogrammed the impacted listing the extreme percentile came from. This infant now has full birth date, which impacts date of assessment, age at assessment, and percentiles in the attached corrected L22, L25, and L25_adhoc (please refer to pages 5-9 attached to this response document). L25 growth percentiles were corrected as the age of infant for follow-up was not 365 days old, but only 97 days. The values for age-specific growth percentiles have been updated, and the infant should no longer be considered as part of 12-month follow-up data. The CSR has not been updated or appended. The mother of the infant was enrolled into the Alternative arm of the registry on 25-Oct-2016. She was treated with HyQvia between 18-Nov-2015 and 04-Apr-2016. The monthly dose of immunoglobulin was 30 g. The date of the last menstruation period was 08-Mar-2016. She gave a live birth. The gestational age at birth was 38 weeks. The male infant had normal length (48 cm), weight (3.11 kg) and head circumference (34.5 cm) at birth. The APGAR scores were 9, 10 and 10 at 1 min, 5 min and 10 min after birth, respectively. The infant was enrolled on 07-Feb-2017, a few months after his birth. We have available follow-up data on growth and development at 97 and 187 days following his birth . At 97 days old the length (57 cm), weight (6.27 kg) and head circumference (38.7 cm) were indicated as normal. No available measurement data at 187 days old. However, at both follow-up visits there were no reports of missed developmental milestones. The infant was discontinued from the study on 08-Feb-2018. The reason for the early termination was subject withdrawal by the parents/legal guardian.

Assessment of the MAH's response

The MAH states that the unusual measurements of the infant were caused by a miscalculation of the actual age of the infant at the time of follow up. Instead of 365 days of age, the infant was apparently only 97 days old. The MAH did not explain why this deviation was considered "normal" in the original report. Furthermore, the MAH states that the infant was born with a normal length (48 cm) and updates the date of enrolment/assessment reported in the study report. In addition, the MAH updated also the dates of enrolment/assessment for all other infants, which were apparently incorrect in the submitted study report. Both data accuracy and presentation could have been improved in the study report. As stated earlier, the small sample size of study 161301, incomplete follow-ups and missing data points do not allow for drawing any reliable conclusions.

Question 2 The MAH is encouraged to investigate participation in registries that aim to assess outcome of drug exposure during pregnancy (cf. EUROCAT network). The MAH is kindly asked to comment upon.

Summary of the MAH's response
The MAH is investigating the feasibility of participating in registries that aim to assess outcome of drug exposure during pregnancy. As suggested by the PRAC in page 14 of the assessment report, the MAH commits to presenting and following up on any cases of drug exposure during pregnancy in future PSURs as cases of special interest.

Assessment of the MAH's response
The MAH states that the feasibility of participating in registries that aim to assess outcome of drug exposure during pregnancy is investigated. Cases of drug exposure during pregnancy will be presented as cases of special interest in future PSURs.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

RMP aspects

Question 3 The MAH is asked to submit an updated RMP addressing the following issues:

a. In Module SVII, it should be stated that while the limited data available does not suggest a different safety profile, study 161301 enrolled so few participants that no reliable conclusions can be drawn.

b. The number of women included in the study and the fraction tested for anti-rHuPH20 antibodies should be clearly stated.

c. The pharmacovigilance plan (RMP part III) lists ongoing and planned pharmacovigilance activities and since study 161301 was completed, it should not be included in this part of the RMP any longer.

d. In annex 2, the change in the subsection "Safety concerns addressed" for study 161301 was updated but should represent the original concern addressed at the start of the study and should be undone.

Summary of the MAH's response

The MAH has updated the RMP (version 12.1) accordingly to reflect the suggestion made by the PRAC.

Assessment of the MAH's response

The MAH submitted an updated RMP. In Module SVII, the MAH included the proposed phrasing that no reliable conclusions can be drawn from study 161301 due to the small sample size but kept and expanded the wording that the study "confirmed no evidence of a different safety profile in pregnant and/or breast-feeding women". Please remove this wording within the next RMP revision. In table SIV.2, the MAH newly added a statement on median follow-up time of 100 weeks for infants in study 161301. Please remove this wording within the next RMP revision as it appears not accurate in view of incomplete and fragmented data (cf. comment to question 5 below).

Issue considered resolved for now.

Question 4 The information on educational material as additional risk minimisation measure should be revised to make the objectives, target audiences and intended content clearer (RMP part V.2 and annex 6). HCPs prescribing the product need to be made aware of the risk of medication errors and the importance to ensure that their patients understand the correct sequence of the HyQvia administration and HCP-directed education material could support HCPs in training patients. Moreover, material for patients may help to remember the correct sequence and technique. Please submit an updated RMP.

Summary of the MAH's response
The MAH has updated the RMP (version 12.1) accordingly to reflect the suggestion made by the PRAC of clarifying objectives, target audience, and intended content of the educational materials. As originally suggested by the MAH in the RMP and also agreed by the PRAC, a detailed review of related reports will be done with the next PSUR with regards to the proposed effectiveness evaluation.

Assessment of the MAH's response

The MAH has updated the RMP and clarified objectives and target audiences of the educational materials. Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

SmPC aspects

Question 5 In summary, the limited sample size of the pregnancy registry precludes any scientific robust conclusion. The proposed revision of section 4.6 of the SmPC therefore needs to be revised substantially.

Summary of the MAH's response
Please refer to the updated Product Information under section 1.3.1 and as tracked Word file in the working folder.
In accordance with the PRAC recommendation the update of section 4.6 of the SmPC has been shortened. Additional information on the pregnancy outcomes has been added because Takeda believes those data are one of the most relevant information from the registry which can help clinicians and patients to make informed decisions regarding the use of HyQvia during pregnancy. The median follow-up time from enrollment in infants has been added to the text. The calculation of the infants' median follow-up time has been attached to this response document (Listing # 1, attached to this response document, page 10).

Assessment of the MAH's response

The MAH submitted a revised Product Information and introduced most requested changes as well as information on pregnancy outcomes, which is acceptable. However, the statement that the growth and development of infants were followed for up to 2 years post-delivery was not removed as requested but only rephrased with the same meaning (infants were followed for a median of 100 weeks). As indicated previously, this appears not acceptable in view of the incomplete and fragmented data, which does not allow for drawing conclusions on the physical and neurological development of infants post maternal HyQvia exposure during pregnancy. For example, at the 12-month follow-up, weight, length and head circumference information was available in 2 infants, and included in the 12-month follow-up due to a data base error (cf. question 1). At 18-months follow-up, this information was available in 1 infant, and at 24-months again for only 1 infant. In line with this, the median follow-up duration based on available information on length and weight would be 97 days instead of almost 2 years. In conclusion, the sentence "A total of 7 infants were enrolled in this study and followed for a median of 100 weeks." should be deleted entirely from the SmPC section 4.6.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

11. List of outstanding issues

1. The proposed update of the SmPC section 4.6 does not at all reflect the incomplete and fragmented follow up data of study 161301 with regard to the infants and is not considered acceptable (cf. comment to question/response 5). Therefore, the sentence "A total of 7 infants were enrolled in this study and followed for a median of 100 weeks." in section 4.6 should be deleted from the SmPC. Please submit the updated SmPC.

Summary of the MAH's response
In accordance with PRAC recommendation, the sentence has been deleted.

Assessment of the MAH's response

The MAH submitted an updated Product Information and introduced the requested change.

Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.