EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/432236/2020
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: HyQvia

International non-proprietary name: human normal immunoglobulin

Procedure No. EMEA/H/C/002491/II/0056

Marketing authorisation holder (MAH) Baxalta Innovations GmbH

Note

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

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
CHMP	Committee for Medicinal Product for Human Use
EU	European Union
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IGI 10%	Immune Globulin Infusion (Human) 10% Solution (IGIV 10% may be used to refer to IGI 10% administered intravenously; IGSC 10% may be used to refer to IGI 10% administered subcutaneously)
IGIV/IVIg	Immune globulin administered intravenously
IGSC/SCIg	Immune globulin administered subcutaneously
fSCIG	facilitated subcutaneous immunoglobulin
IV	Intravenous(ly)
MAH	Market Authorisation Holder
PID	Primary immunodeficiency
rHuPH20	Recombinant human hyaluronidase
SAE	Serious adverse event
SC	Subcutaneous(ly)
SID	Secondary immunodeficiency
SmPC	Summary of product characteristics

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Baxalta Innovations GmbH submitted to the European Medicines Agency on 10 February 2020 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for HyQvia to substitute the indication of:

- replacement therapy in hypogammablobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia and multiple myeloma and hypogammaglobulinaemia in patients with HSCT,

by the new wording:

- replacement therapy 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.

As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 14 November 2019 (EMEA/H/SA/1170/4/2019/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Andrea Laslop

Timetable	Actual dates
Submission date	10 February 2020
Start of procedure:	29 February 2020
CHMP Rapporteur Assessment Report	23 April 2020
CHMP Co-Rapporteur Assessment Report	23 April 2020
PRAC Rapporteur Assessment Report	23 April 2020
PRAC members comments	6 May 2020
PRAC Outcome	14 May 2020
CHMP members comments	18 May 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	25 May 2020
Request for supplementary information (RSI)	28 May 2020
PRAC Rapporteur Assessment Report	26 June 2020
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
CHMP Rapporteur Assessment Report	13 July 2020
PRAC Outcome	09 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur Assessment Report	N/A
Opinion	23 July 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Therapeutic indication

HyQvia is approved for the following indications, as listed in the HyQvia SmPC. Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production (primary immunodeficiency disease, PID),

As well as in SID including,

- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients.
- Hypogammaglobulinaemia in patients pre- and post-allogeneic hematopoietic stem cell transplantation (HSCT).

Claimed Indication

HyQvia can be used as replacement therapy in SID in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF: failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines) or serum IgG level of <4 g/l).

Rationale

HyQvia's safety and efficacy in PID have been established based on relevant clinical data (biological, pharmacokinetic, efficacy and safety data). A marketing authorization for these indications as well as for specific SIDs was granted throughout the EU in 2013. These SIDs, as listed in the guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 rev. 3 dated 2018) in effect, already encompassed a major part of the SID patient population. HyQvia produces a similar reduction in the number of serious bacterial infections to that seen with other immunoglobulin products thus, the key elements required for alignment of its SID indication are considered sufficient.

Medical Significance

SIDs are more frequent than primary immune deficiencies, and are not genetic in nature but are caused by external factors, such as certain haematological cancers as leukemia, CLL, MM, human immunodeficiency virus (HIV), certain chronic illnesses such as diabetes, the absence of a spleen, malnutrition, or immunosuppressive medication or HSCT/chemotherapy (Chinen and Shearer, 2010[1]).

Clinical Symptoms and Diagnostic Criteria

SIDs (Chinen and Shearer, 2010) are clinically manifested by an increased frequency or complications of common infections and sporadically by the occurrence of opportunistic infections. They have a wide spectrum of presentation, depending on the extent of offending external conditions and on host susceptibility. If a specific SID is suspected clinically, testing should focus on the underlying condition (e.g., diabetes, HIV infection, cystic fibrosis, primary ciliary dyskinesia).

Etiology, Incidence and Prevalence

SID is relatively common, and worldwide the most prevalent causes include malnutrition and advancing age. The etiologies of SID can be loosely grouped into those caused by the related abnormalities of general health, underlying disease, barrier integrity or iatrogenic influences, e.g. immunosuppressive treatment. Issues with general health that result in SID include malnutrition, advancing age, smoking and alcohol. Underlying diseases that cause SID include hematological malignancies such as chronic lymphocytic leukemia and multiple myeloma, allogeneic bone marrow transplantation, splenectomy/hyposplenism and some infections (e.g. HIV, Philip Bright P. and Richter A., 2017[2]).

[1] Chinen, J. & Shearer, W. T. 2010. Secondary immunodeficiencies, including HIV infection. J Allergy Clin Immunol, 125, S195-S203.
[2] Philip Bright P. & Richter A. 2017. Immunodeficiency: Secondary. eLS. John Wiley & Sons, Inc.Web Link: http://www.els.net

When evaluating a patient with increased frequency or severity of infections suggesting immunodeficiency, it should be considered that SIDs are far more common than PID. A detailed clinical history might uncover the condition affecting the immune system and exposure to harsh environmental conditions. The specific immune defects and clinical presentation in SIDs are usually affecting both the innate and the adaptive immunity. The immune impairment generally improves with the resolution of the primary condition (Chinen and Shearer, 2010[1]).

2.1.2. About the product

HyQvia (10% human normal immunoglobulin with recombinant human hyaluronidase [rHuPH20]) for subcutaneous (SC) administration, subsequently referred to as HyQvia, is currently licensed in the European Union (EU) for replacement therapy in primary immunodeficiency disorder (PID) and a number of secondary immunodeficiencies (SIDs) including chronic lymphocytic leukemia, multiple myeloma, post-allogeneic bone marrow transplantation. HyQvia is a facilitated SC immunoglobin (facilitated IGSC) due to the rHuPH20 component. The immunoglobulin part of HyQvia (IGI 10% solution) is identical to the product KIOVIG, which is a licensed intravenous IGI 10% (IGIV) in Europe. Both products have the same manufacturing process. The main differences between KIOVIG and HyQvia are the route of administration (IV vs SC) and the administration of rHuPH20 before SC infusion of the IGI 10% component. rHuPH20 increases the tissue dispersion and absorption of IGI 10% and facilitates increased flow rates and volumes of SC delivery compared with SC administration without rHuPH20. With rHuPH20 as a facilitator for absorption, IGI 10% in HyQvia is more than 90% bioavailable (at least 10-20% higher than other IGSC products), providing nearly equivalent systemic exposure to IGIV. The HyQvia clinical development program (

Table 1) includes 4 completed studies investigating the safety, tolerability efficacy, and pharmacokinetics of IGSC 10% and rHuPH20 treatment in pediatric, adolescent and/or adult subjects with PID (Studies 160602, 160603, 160902 and 161101). The Market Authorisation Holder (MAH) also conducted a study to investigate the pharmacokinetics, tolerability, and efficacy of IGI 10% given IV and SC without rHuPH20 to obtain comparative data in subjects with PID (Study 160601). In addition, 2 studies were conducted to assess safety, tolerability, effectiveness, infusion pressure, and flow rates of IGSC 10% and rHuPH20 in healthy volunteers (Studies 161001 and 170901).

Table 1 Completed clinical studies in the development program for HyQvia (Ig10% and rHuPH20)

Study	Title	Phase	Region	Subjects
160601	Tolerability and Pharmacokinetic Comparison of IGIV 10% Administered IV or SC in Subjects with PID	2/3	US	49 paediatric, adolescent and adult subjects with PID
160602†	Ph I/II Determination of the Dose of rHuPH20 Required Enabling up to 600 mg/kg body weight of IGIV 10% to be Administered SC in a Single Infusion Site in Subjects with PID	1/2 pilot	US	11 adults with PID
160603	Efficacy, Tolerability and Pharmacokinetic Comparison of IGIV 10% Administered IV or SC Following Administration of rHuPH20 in Subjects with PID	3 Pivotal	US, Canada	87 paediatric, adolescent and adult subjects with PID
160902	Long-term Tolerability and Safety of Immune Globulin Subcutaneous (IGSC 10%) Solution Administered Subcutaneously Following Administration of Recombinant Human Hyaluronidase (rHuPH20) in Subjects with PID	3 Follow-up study	US, Canada	66 paediatric, adolescent and adult subjects with PID
161101*	Tolerability, Safety and Administration Mode Evaluation of rHuPH20-facilitated Subcutaneous Treatment with Immune Globulin Infusion (Human) 10% in Subjects with PID	2/3	US	37 paediatric, adolescent and adult subjects with PID
161001	A Phase 1 Study for the Evaluation of the Effectiveness of rHuPH20 in Enhancing the Subcutaneous Administration of Immune Globulin Subcutaneous (Human) 10% Solution (IGSC 10%) in Healthy Volunteers	1	US	53 healthy adult volunteers
170901 Part 4	A Phase 1 Study of IGSC Administered Either Alone or In Combination With rHuPH20 Permeation Enhancer for the Evaluation of Safety, Tolerability, and Optimal rHuPH20-to-IGSC Dose Ratio in Healthy Volunteers	1	US	12 healthy adult volunteers

* Clinical study 161101, conducted in the US, investigated the tolerability, safety, and administration mode of rHuPH20-facilitated subcutaneous treatment with IGI 10% in subjects with PID. HyQvia treatment was terminated early due to FDA request. There were 25 subjects who completed this study
† Clinical study 160602 was performed to determine the feasibility and dose of rHuPH20 required to enable SC administration of up to 600 mg/kg of IGI 10% in a single infusion site in subjects with PID.
Abbreviations: IGI = immune globulin infusion; IGIV = immune globulin infusion (human) for intravenous administration; IGSC = immune globulin subcutaneous (human); PID = primary immune deficiency; rHuPH20 = recombinant human hyaluronidase; SC = subcutaneous(ly); US = United States.

In the EU, HyQvia was approved for the indications of the Core SmPC through a centralized procedure (registration number EU/1/13/840/001-005). The European Commission granted a marketing authorization valid throughout the EU on 16th May 2013.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Two revised EU guidelines for intravenous immunoglobulins came into effect in January 2019:

- Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWF/94038/ 2007 Rev 5; Committee for Human Medicinal Products (CHMP), 2018).

- Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration, 28 June 2018 (EMA/CHMP/BPWP/94033/2007 rev. 3, CHMP, 2018)

The revised guidelines include a rewording of the SID indication for IGIV to extrapolate the indication to all SIDs if the efficacy in PID is established. These guidelines only apply to IGIV. However, it has been demonstrated that Igs are effective independent of the mode of administration and both IGIV and IGSC (including facilitated IGSC) can treat subjects with diseases such as SID.

In September 2019, the MAH sought scientific advice from the (CHMP (EMEA/H/SA/1170/4/2019/II) regarding the update of the Product information (PI) for HyQvia for its compliance and harmonization with the changes introduced in the two aforementioned guidelines, specifically, the change to the definition of SIDs. In November 2019, the CHMP provided a favorable opinion on the proposed rewording of the HyQvia indication. The main changes comprise a revision of the definition of SID and a clarification of dose adjustment based on patient's body weight and addition of a recommended dose and dosing regimen for SIDs.

With this application, the MAH intends to align the wording for the already approved SID indications in the HyQvia SmPC with the wording of the Guideline on core SmPC for human normal immunoglobulin for intravenous administration. An analysis of the existing literature and summary of confirmatory data on the efficacy of HyQvia are provided to support the alignment of the SID indication. In addition, dose justifications and adjustments have been made according to the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IGIV). Based on the CHMP advice provided for HyQvia, the MAH proposes an update of the Summary of Product Characteristics (SmPC) affecting Section 4.1 "Therapeutic Indications" and Section 4.2 "Posology and Method of Administration" as well as of Section 1 of the Patient Leaflet "What HyQvia is used for".

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Under the current application for a Type II variation to reword and expand the definition of secondary immunodeficiencies in the Patient Information, the MAH is waiving an ERA report per the guideline (EMEA/CHMP/SWP/4447/00 corr 2). Considering that HyQvia contains a naturally occurring protein as the active pharmaceutical ingredient, HyQvia is not expected to pose a risk to the environment and the absence of ERA studies is considered justified.

2.2.2. Conclusion of the non-clinical aspects

No new non-clinical data have been submitted and the pre-clinical section 5.3 of the SmPC remains unchanged. This is considered acceptable by CHMP.

2.3. Clinical aspects

2.3.1. Pharmacodynamics

The following changes or additions are made to dosing recommendations in the proposed revised SmPC based on new recommendations provided in Guideline EMA/CHMP/BPWP/94038/2007 (CHMP, 2018) and in alignment with the KIOVIG SmPC:

• Addition: *Dose based on bodyweight may require adjustment in underweight or overweight patients.*

• Addition: *Specific dosing regimen for secondary immunodeficiencies: the recommended dose is 0.2-0.4 g/kg every three to four weeks.*

• Addition: *IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.*

Primary and secondary pharmacology

A total of 4 studies were previously completed with HyQvia in subjects with PID (studies 160602 and 160603,160902 and 161101) (Wasserman et al., 2016a[3], Wasserman et al., 2016b[4], Wasserman et al., 2012[5]). As a guideline, the proposed recommended starting dose of rHuPH20-facilitated SC administered IGI 10% is 300 to 600 mg/kg body weight (BW) per month preceded by a minimum of 75 U of rHuPH20 per gram IgG, infused at 3- or 4-week intervals. For patients previously on IV IgG replacement therapy, administration should start at the same dose and frequency; for patients previously on regular SC replacement therapy, the initial monthly IgG dose should be the same as for SC treatment, but adjusted to 3- or 4-week intervals. HyQvia was shown to have nearly equivalent total systemic exposure as represented by the area under the curve (AUC) as well as trough levels of serum IgG as compared to IGIV based on results from clinical studies 160602 and 160603, wherein IGI 10% was administered either SC at 108% of IV dose with rHuPH20 (HyQvia) or IV without rHuPH20 (KIOVIG) in subjects with PID. In the phase 3 Study 160603, the geometric mean ratio (SC/IV) of AUC over a dosing interval (AUC0-τ) for IgG was found to be 93.3%, with a 90% confidence interval (CI) of 91.4% to 95.2%. The median peak concentration (Cmax) of serum IgG was lower after HyQvia than after IV infusion (15.5 g/L vs 21.9 g/L) while the median time to reach Cmax was longer (Tmax: 5.0 vs 0.1 days).

2.3.2. Discussion on clinical pharmacology

No new pharmacological data was submitted.

The proposed dosing is aligned with the KIOVIG posology for the treatment of secondary immunodeficiencies and with the Guideline EMA/CHMP/BPWP/94038/2007(CHMP, 2018). Based on the proven bioequivalence for HyQvia to Kiovig regarding the exposure (AUC0-t in pivotal trial 160603), this

[3] Wasserman, R. L., Melamed, I., Kobrynski, L., Pck, J., Gupta, S., Doralt, J., Sharkhawy, M., Engl, W., Leibl, H., Gelmont, D. & Yel, L. 2016a. Recombinant human hyaluronidase facilitated subcutaneous immunoglobulin treatment in pediatric patients with primary immunodeficiencies: long-term efficacy, safety and tolerability. *Immunotherapy,* 8, 1175-1186

[4] Wasserman, R. L., Melamed, I., Stein, M. R., Engl, W., Sharkhawy, M., Leibl, H., Puck, J., Rubinstein, A., Kobrynski, L., Gupta, S., Grant, A. J., Ratnayake, A., Richmond, W. G., Church, J., Yel, L. & Gelmont, D. 2016b. Long-term tolerability, safety, and efficacy of recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulin for primary immunodeficiency. J Clin Immunol, 36, 571-582.

[5] Wasserman, R. L., Melamed, I., Stein, M. R., Gupta, S., Puck, J., Engl, W., Leibl, H., McCoy, B., Empson, V. G., Gelmont, D., Schiff, R. I. & IGSC, r. S. G. 2012. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. J. Allergy Clin. Immunol, 130, 951-957.e11.

is considered acceptable by CHMP and in accordance with the output from the Scientific Advice (EMEA/H/SA/1170/4/2019/II).

The following dosing recommendations are added in SmPC Section 4.2:

- Dose based on bodyweight may require adjustment in underweight or overweight patients.
- For secondary immunodeficiencies, the recommended dose is 0.2-0.4 g/kg every three to four weeks. IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

2.3.3. Conclusions on clinical pharmacology

HyQvia exhibited nearly complete bioavailability and similar steady-state trough levels of serum IgG to KIOVIG. Thus, HyQvia is considered by CHMP a comparable treatment option to KIOVIG.

The revised dosing recommendations are appropriate and agreed by CHMP.

2.4. Clinical efficacy

2.4.1. Main study

Clinical Studies of IGI 10% with and without rHuPH20 in Subjects with PID Serious Acute Bacterial Infections

The rate of validated acute serious bacterial infections per subject-year during IGSC 10% and rHuPH20 treatment was the primary efficacy endpoint in Studies 160603 and extension Study 160902 (Wasserman et al., 2016b, Wasserman et al., 2012). They were among the key variables in Study 161101. The rate of validated serious acute bacterial infections per subject-year was 0.025 (upper limit of 99% CI: 0.046) during IGSC 10% and rHuPH20 treatment in Study 160603, 0.020 (upper limit of 99% CI: 0.045) during IGSC 10% and rHuPH20 treatment in Study 160902, and 0 (upper limit of 99% CI: 0.471) in Study 161101. Thus, in all studies, the rates were well below 1.0 validated acute serious bacterial infections/subject/year, the threshold specified as providing substantial evidence of efficacy by the relevant regulatory guidelines (CHMPe, 2018, Food and Drug Administration (FDA), 2008). These rates are comparable to the rate observed for SC administered IGI 10% alone in Study 160601 (rate: 0.067 upper limit of 99% CI: 0.134) (Wasserman et al., 2011[6]) and IV administered IGI 10% (upper limit of 95% CI: 0 to 0.060) (Church et al., 2006[7]). These results demonstrate that IGSC 10% and rHuPH20 treatment provides comparable protection from serious acute bacterial infections to SC administered IGI 10% alone or to IV-administered IGI 10%.

[6] Wasserman, R. L., Melamed, I., Kobrynski, L., Strausbaugh, S. D., Stein, M. R., Sharkhawy, M., Engl, W., Leibl, H., Sobolevsky, L., Gelmont, D., Schiff, R. I. & Grossman, W. J. 2011. Efficacy, safety, and pharmacokinetics of a 10% liquid immune globulin preparation (GAMMAGARD LIQUID, 10%) administered subcutaneously in subjects with primary immunodeficiency disease. J Clin Immunol, 31, 323-331.

[7] Church, J. A., Leibl, H., Stein, M. R., Melamed, I. R., Rubinstein, A., Schneider, L. C., Wasserman, R. L., Pavlova, B. G., Birthistle, K., Mancini, M., Fritsch, S., Patrone, L., Moore-Perry, K. & Ehrlich, H. J. 2006. Efficacy, safety and tolerability of a new 10% liquid intravenous immune globulin (IGIV 10%) in patients with primary immunodeficiency. J Clin Immunol, 26, 388-395.

All Infections

The rates of all infections per subject-year were determined in Studies 160601, 160602 and 160603 and results were integrated across the studies. In Study 160601, subjects received IGI 10% IV in Study part 1 and IGI 10% SC in Study Part 2 and Part 3 and in the Study Extension. Comparative data were obtained on the pharmacokinetics, tolerability and efficacy of IGI 10% given IV and SC without rHuPH20. A subset of 31 subjects who participated in Study 160601 also participated in Study 160603.

Study 160603, consisted of 2 study epochs: in Study Epoch 1 subjects received IV treatment with IGI 10%, and in Study Epoch 2 IGI 10% was infused SC after administration of rHuPH20 at 3- or 4-week treatment intervals. In Study 160602, subjects received IGSC 10% with rHuPH20. This study was not designed to determine the efficacy of IGI 10% treatment. Infections were reported as adverse

events (AEs) and the number and types of infections were determined.

It should be noted that in Studies 160601 and 160603, the period of IV exposure to IGI 10% was substantially shorter than for IGI 10% administered SC with or without rHuPH20. The point estimates were 3.02 infections/subject/year (95% CI: 2.56 to 3.54) for HyQvia, 4.00 (95% CI: 3.13 to 5.02) for IGI 10% administered SC alone and 4.42 (95% CI: 3.52 to 5.47), for IGI 10% administered IV (HyQvia).

Under IGSC 10% and rHuPH20 treatment in Study 160902, the rate of infections per subject-year was 2.86 (95% CI: 2.36 to 3.43). In an integrated analysis the overall annual rate of infections while on IGSC 10% and rHuPH20 treatment in Study 160603 and in the extension Study 160902 was 2.99 (95% CI: 2.60 to 3.42) (Wasserman et al., 2016b). In Study 161101, the rate of all infections per year while on IGSC 10% and rHuPH20 was 2.45 (95% CI: 1.55-3.66).

The pooled results confirm that the rate of infections during IGSC 10% and rHuPH20 treatment was as low as during IGI 10% treatment administered IV or SC without rHuPH20.

Efficacy of IGSC Products in Subjects with SID from published data

Published data on the response to Ig replacement with IGSC 10% and rHuPH20 in subjects with SID indicate that IGSC 10% with rHuPH20 is effective in decreasing the incidence of infections in subjects with SID. In a single-center retrospective analysis of 33 subjects with SID who receive IGSC 10% and rHuPH20 as replacement therapy, 7 episodes of infection were reported in 6 subjects during HyQvia treatment. IgG trough levels were below 600 mg/dl at the time of infection in all 6 subjects. After Ig dose

adjustment to increase IgG trough levels, no new infection occurred (Dimou et al., 2018[8]). Furthermore, efficacy of IGSC replacement therapy in subjects with SID was also reported with a IGSC 20% product in a randomized but not blinded study. A statistically lower number of infections were reported in the 24 subjects treated with IGSC 20% in comparison with the 22 subjects in the control group who did not receive Ig replacement therapy (Vacca et al., 2018[9]).

2.4.2. Discussion on clinical efficacy

According to results of Studies 160603, 160902 and 161101 efficacy of SCIg/fSCIg compared with IVIg was proven in adult and paediatric PID patients. The rates of validated acute serious bacterial infections per subject-year were significantly below the threshold specified as providing substantial evidence of efficacy. Regarding the rates of all infections, HyQvia provided a significant clinical benefit

[8] Dimou, M., Iliakis, T., Maltezas, D., Bitsani, A., Kalyva, S., Koudouna, A., Kotsanti, S., Petsa, P., Papaioannou, P., Kyrtsonis, M. C. & Panayiotidis, P. 2018. Efficacy- safety of Facilitated Subcutaneous Immunoglobulin in Immunodeficiency Due to Hematological Malignancies. A Single-Center Retrospective Analysis. Anticancer Res, 38, 4187-4191.
[9] Vacca, A., Melaccio, A., Sportelli, A., Solimando, A. G., Dammacco, F. & Ria, R. 2018. Subcutaneous immunoglobulins in patients with multiple myeloma and secondary hypogammaglobulinemia: a randomized trial. Clin Immunol, 191, 110-115.

across all conducted studies, too. As to PID, a comparable protection from serious bacterial infections and general infections is acknowledged by CHMP. As already pointed out in the EMA Scientific Advice, the provided literature has shortcomings as to the analysed numbers of patients suffering from SID. However, as the indication hypogammaglobulinaemia caused by oncological diseases or HSCT was already included in the SmPC and thereby encompasses a major part of the SID patient population, the proposed rewording of the HyQvia indication is acceptable to the CHMP.

2.4.3. Conclusions on the clinical efficacy

The revised guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 Rev. 5) includes a rewording of the SID indication for IVIg. Even if this guideline applies to IVIg, it has been demonstrated that Igs are effective independent of the mode of administration, and both IVIg and SCIg/fSCIg are effective in treating subjects with SID. The extrapolation of the indication to all SIDs is endorsed by CHMP since the efficacy in PID is established. Moreover, the beneficial effects of SCIg/fSCIg are substantiated by the provided literature.

The proposed rewording of the HyQvia indication is thus agreed by CHMP:

HyQvia can be used as replacement therapy in SID in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF: failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines) or serum IgG level of <4 g/l.

2.5. Clinical safety

Safety of IGSC products in Subjects with PID

Related Serious Adverse Events

No related serious adverse events (SAEs) occurred in 5 studies evaluating different modes of administration of IGI 10% (IV, SC with/without rHuPH20) in paediatric, adolescent and adult subjects with PID. Two related SAEs were reported, in Study 170901 Part 4: in one healthy volunteer after receiving IGSC 10% with formulation buffer control and in another healthy volunteer who had been administered IGSC 10% with rHuPh20. These events were instances of hemolytic anemia that were assessed by the investigator as possibly being related to the investigational products, with an alternative etiology of viral infection. Asymptomatic hemolysis and significantly decreased hemoglobin were assessed by a number of parameters in Studies 160603, 160902, and 161101 including direct Coomb's test, haptoglobin, lactic dehydrogenase (LDH), urinary hemosiderin, and reticulocyte count, and no confirmed or suspected cases were reported. No other significant safety concerns were raised regarding IGSC 10% and rHuPH20 administered to subjects with PID or healthy volunteers.

Related Non-Serious Adverse Events

The nature of adverse drug reactions (ADRs) was similar for IGSC 10% treatment with and without rHuPH20 in Studies 160601 and 160603; the most commonly reported reactions included infusion site pain, headache, and infusion site erythema.

• In subjects who received IGSC 10% and rHuPH20, ADRs that occurred at rates of >0.05 per infusion in any study were: infusion site pain, infusion site erythema, infusion site swelling, injection site pruritus, headache, infusion site pruritus, nausea, infusion site discoloration, infusion site induration, injection site pain, injection site discoloration, and skin discoloration.

• In subjects who received IGIV 10%, ADRs that occurred at rates of >0.05 per infusion were: headache, urticaria, vomiting, chills, pain, peripheral edema, and back pain.

• ADRs to IGSC 10% alone were palpitations, infusion site pain, infusion site pruritus, infusion site swelling, infusion site induration, infusion site discoloration, injection site discoloration, injection site pain, and leucopenia, occurring at rates of >0.05 per infusion (CSR 160601 Table 14.3.2-15). In Study 160902, the only related AE that occurred at a rate per infusion >0.05 during long-term treatment with IGSC 10% and rHuPH20 was infusion site pain.

In Study 161101, the most common AEs related to IGSC 10% and rHuPH20 were infusion site pain, infusion site erythema, infusion site swelling, infusion site pruritus, local swelling, pyrexia and headache. Thus, in line with published data, SC infusions of IGI 10% with or without rHuPH20 were more frequently associated with local ADRs than IV infusions of IGI 10%, but were

associated with a lower rate of systemic ADRs (Church et al., 2006[7], Gardulf, 2007[10], Gardulf et al., 1995[11], Gustafson et al., 2008[12]).

Safety of IGSC Products in Subjects with SID from published data

Clinical post-marketing experience with IGSC 10% and rHuPH20 has recently been reported from a retrospective single-center analysis in 33 subjects with SIDs due to hematological malignancies who were treated with HyQvia (Dimou et al., 2018[8]). The incidence of AEs deemed as related to HyQvia by the investigator was low (9%) in this study and all ADRs were assessed as mild (grade 1).

Adverse reactions were also local in nature and mild in most subjects in the IGI SC 20% group in a prospective, controlled, randomized but not blinded study in subjects with multiple myeloma and secondary hypogammaglobulinemia randomly assigned to treatment with a IGSC 20% product (Arm A, n = 24) or to the control group (no Ig treatment, Arm B, n = 22). For 3/24 subjects randomized to IGSC 20% treatment, grade 3/4 ADRs were reported (2 instances of pain and inflammatory reaction at the site of injection and one extensive allergic skin reaction), that required treatment discontinuation

(Vacca et al., 2018[9]).

Safety of rHuPH20

Fifteen (15) of the 83 subjects exposed to HyQvia in studies 160603 and 160902 developed at least a single positive titer (≥1:160) of antibodies capable of binding to rHuPH20. In all subjects, titers declined to baseline, or titers seen in PH20 naïve subjects/normal population despite continued exposure to HyQvia Based upon data available to date, the incidence of treatment emergent rHuPH20-reactive

binding antibodies was low and neutralizing antibodies have not been observed in any subjects. There has been no evidence of a lack of treatment effect when rHuPH20-reactive binding antibodies have been detected. In all subjects, antibody titers decreased despite continued treatment. In addition, no clinical signs or symptoms have been associated with positive rHuPH20-reactive binding antibody titers. No investigations (clinical or nonclinical) have implicated rHuPH20-reactive binding antibodies as causal factors for any adverse clinical event.

[10] Gardulf, A. 2007. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. BioDrugs, 21, 105-116.
[11] Gardulf, A., Andersen, V., Björkander, J., Ericson, D., Frøland, S. S., Gustafson, R., Hammarström, L., Jacobsen, M. B., Jonsson, E., Möller, G., Nyström, T., Søeberg, B. & Smith, C. I. E. 1995. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet,* 345, 365- 369.
[12] Gustafson, R., Gardulf, A., Hansen, S., Leibl, H., Engl, W., Linden, M., Muller, A. & Hammarström, L. 2008. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. Clin Exp Immunol, 152, 274-279.

Thus, based on clinical evidences the safety profile of subjects who developed antibodies to rHuPH20 is comparable to the safety profile of subjects with negative titer with regard to the nature and rate of AEs observed during the entire exposure to HyQvia.

2.5.1. Discussion on clinical safety

The nature of ADRs was similar for IGSC 10% treatment with and without rHuPH20 in patiens with PID in Studies 160601 and 160603; the most commonly reported reactions included infusion site pain, headache, and infusion site erythema. In line with published data, SC infusions of IGI 10% with or without rHuPH20 in patients with PID were more frequently associated with local ADRs than IV infusions of IGI 10%, but were associated with a lower rate of systemic ADRs (Church et al., 2006[7], Gardulf, 2007[10], Gardulf et al., 1995[11], Gustafson et al., 2008[12]). In addition, published data support the safety of IGSC as replacement therapy in subjects with SID.

No new safety concerns arose during the post-marketing period. Therefore, both IVIg and SCIg/fSCIg are safe in treating subjects with SID.

2.5.2. Conclusions on clinical safety

The use of HyQvia in patients with SID is agreed by CHMP from a safety perspective.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.1 is acceptable. The CHMP endorsed the Risk Management Plan version 10.1 with the following content:

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 the infusion period. SmPC Section 4.8 PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: 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 hydrated before use of immunoglobulins. SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Expedited reporting of all TEEs. TEE questionnaire. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL Section 4 Additional risk minimisation measures: 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 measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Important potential risks:	Routine risk minimisation	Routine pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Spread of localised infection	measures: SmPC Section 4.2 PL Section 2 Additional risk minimisation measures: None.	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: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Missing information: Lack of 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 measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Study 161301 (Category 3).
Missing information:	Routine risk minimisation	Routine pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years	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.	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)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template version 10.1, which were reviewed and accepted by the CHMP.

The conditions or restrictions with regard to the safe and effective use of the medicinal product are also updated to include the ongoing non-interventional post-authorisation safety study on the long-term safety of HyQvia in subjects treated with HyQvia. This study was missing from Annex II whereas it is a Category 1 study in the RMP.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

HyQvia's safety and efficacy in PID have been established based on relevant clinical data (biological, pharmacokinetic, efficacy and safety data). HyQvia is already authorised for these indications as well as for specific SIDs. HyQvia produces a similar reduction in the number of serious bacterial infections to that seen with other immunoglobulin products.

Therefore, taking into consideration that HyQvia was shown to be safe and efficacious in paediatric and adult patients with PID, the final clinical manifestations for PID and SID result in severe infections due to hypogammaglobulinaemia requiring replacement therapy and that the IGSC core SmPC wording already emcompassed a major part of the SID patient population (CLL, MM and HSCT with hypogammablobulinaemia), a favourable risk-benefit profile of HyQvia has been demonstrated to extend the indication of SID as defined in the latest core SmPC for IGIV (EMA/CHMP/BPWP/94038/ 2007 Rev 5; CHMP, 2018).

Therefore, the therapeutic indication in SmPC Section 4.1 and dosing recommendation SmPC Section 4.2 are updated in accordance with the applicable core SmPC for IGIV (EMA/CHMP/BPWP/94038/ 2007 Rev 5; CHMP, 2018). This is considered adequate by CHMP to provide the prescriber with sufficient information to enable optimal safety with regards to HyQvia's administration.

3.1. Conclusions

The overall B/R of HyQvia is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication for HyQvia in order to align the wording for the already approved secondary immunodeficiencies indications in the HyQvia SmPC with the wording of the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/ 2007 Rev 5; CHMP, 2018).

As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.1 of the RMP is also agreed.

Furthermore, the PI is brought in line with the latest QRD template version 10.1. As a consequence, Sections 1, 2, 3, 4.2, 4.4, 4.7, 4.8, 5.2 and 6.5 of the SmPC, labelling and package leaflet are updated.

The conditions or restrictions with regard to the safe and effective use of the medicinal product are also updated to include the ongoing non-interventional post-authorisation safety study on the long-term safety of HyQvia in subjects treated with HyQvia, which is a Category 1 study in the agreed RMP.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'HyQvia-H-C-002491-II-0056'

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted).

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information (CCI) in "track changes" and with detailed justification by 07 August 2020. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf.

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 07 August 2020. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. The MAH is reminded that, at the same time as the submission on the eCTD closing sequence mentioned above, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

4. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI:

Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.