

Addendum to Pharmacovigilance Review Memorandum
Office of Biostatistics and Epidemiology/Division of Epidemiology (OBE/DE)

BLA/Supplement Number:	125402/0
Product Name:	HyQvia Immune Globulin Infusion (Human), 10% with Recombinant Human Hyaluronidase
Sponsor:	Baxter Healthcare Corporation, Baxter Bioscience
Indication(s):	Primary immune deficiency (PID) associated with defects in humoral immunity
Date(s):	CBER receipt date: 6/30/2011; Initial ADD: 4/27/2012; Major Amendment: 3/1/2012; New ADD 7/29/2012
Review Priority:	Routine
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1. Introduction

a. Product description

HyQvia (STN125402) is a new product, composed of a currently licensed IgIV, Gammagard Liquid (STN 125105) and recombinant hyaluronidase (rHuPH20). HyQvia is a combination product designed to be given as a sequential subcutaneous infusion of recombinant human hyaluronidase followed by 10% IgIV. The purpose of the hyaluronidase is to “promote the dispersion and absorption of the active therapeutic substance immunoglobulin G (IgG) to increase its bioavailability.” (HyQvia BLA Pharmacovigilance Plan, version 1.0, 23Jun2011 p7) One of the serious limitations of current IgSC therapy is that a limited amount of fluid can be injected at a given site. This necessitates the use of multiple injection sites and weekly therapy. The rHuPH20 component of HyQvia enzymatically dissolves the hyaluronan component of the extracellular matrix, allowing greater dispersion of fluid and larger volumes to be injected at a single site. The advantage to the patient is fewer injection sites and less frequent injections (every 3 to 4 weeks instead of weekly). (Clinical Overview p2)

b. Pertinent regulatory history

i. Prior licensure in the U.S. or other nations

HyQvia is not currently licensed in the U.S., nor in any other country. However, the IgIV used in HyQvia is a U.S. licensed product, Gammagard Liquid. (Gammagard Liquid is marketed under the trade name “Kiovig” in the EU). Hyaluronidase (trade name “Hylenex”) is also a licensed product in the U.S., although the hyaluronidase in HyQvia differs from the currently licensed product in ----(b)(4)---- (HyQvia is -----(b)(4)----- ----(b)(4)-----) and is designed to be administered chronically. In addition, some final product specifications for the hyaluronidase component have been changed.

1. Summary of indications and usage

The proposed indication for HyQvia is the treatment of patients with primary immunodeficiency (PI) associated with defects in humoral immunity (BLA Cover Letter). There are no age specifications in the proposed labeling, but HyQvia was not tested in patients < 2 years of age in the clinical trials. Gammagard Liquid, the Ig component of HyQvia, is approved for use in patient 2 years of age and older. Discussion with the clinical reviewer confirmed that, if approved with the current data, the age indication would be 2 years of age and older. HyQvia is administered subcutaneously.

2. Major post-marketing safety findings

There is no post-marketing data for HyQvia, since it is not currently licensed. However, since this combination product is composed of 2 licensed products, post-marketing data exists for each component.

Gammagard Liquid is an Ig licensed for both IV and SC use for the treatment of primary immune deficiency (PI). The AE profile includes many events common to the IgIV class: hypersensitivity reactions, aseptic meningitis, renal failure, hemolysis, thromboembolic events, TRALI, and interference with laboratory tests (passively transmitted antibodies, positive Coombs test, etc.).¹

Adverse events following Hylenex include allergic/hypersensitivity reactions, the potential to spread local infection (if administered at a site of infection), and local irritation or edema.²

ii. CBER Complete Response letters

None.

iii. Relevant prior advisory committee meetings

None.

c. Objectives/scope of this review

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies, should the product be licensed.

2. Materials reviewed

The following sources of data were reviewed:

a. Routine items

i. Pharmacovigilance plan

Reviewed Version 1.0, dated 23June2011.

ii. Pertinent sections of the BLA

iii. Postlicensure safety data

AERS data for Gammagard Liquid and Hylenex were reviewed.

iv. Input from CBER reviewers

The draft memo from OBRR clinical review Lawrence Landow was reviewed.

v. Medical literature

b. Other items

i. Information received under MOU from Foreign regulatory or public health agencies.

HyQvia was discussed at the FDA-EMA-HC Blood Cluster

Teleconference on 4May2012. I attended this call and reviewed the meeting minutes in preparing this memo. Salient points from this discussion are found in section 4b. of this memo.

3. Pharmacovigilance Plan review

a. Clinical safety database

The safety of HyQvia was evaluated in 5 studies, 2 in healthy volunteers and 3 in patients with primary immune deficiency (PID). A total of 199 patients were enrolled in the clinical development program with 146 HyQvia recipients. Only 1

¹ Gammagard Liquid PI, July 2011 ed.

² Hylenex PI, Mar2012 ed.

of the 5 clinical trials was placebo controlled (4 were open labeled studies) and 1 was a cross-over design that involved switching from IV Gammagard Liquid to SQ HyQvia administration. The length of the follow up observation time ranged from approximately 1 month in study 170901 (which was terminated prematurely), to 2 years in study 160902. Adverse events were monitored using patient diaries and an interview reviewing the patient diary, conducted at the next infusion visit. All adverse events since the previous infusion were recorded but temporally associated adverse events were defined as those occurring within 72 hours after an infusion. The end-of-study visit was conducted one infusion interval (21-28 days) following the last infusion.

Analyses of all serious adverse events in the pooled safety population are described in Table 1. No imbalances were noted, although the number of Gammagard Liquid only recipients was small. There were a total of 26 serious adverse events. All serious AEs, except the 2 cases of hemolytic anemia (described in detail below), were regarded as unrelated by study investigators.

TABLE 1: Serious Adverse Events in the Pooled Safety Database (N = 199)

Adverse Event	HyQvia group (n = 146)	Gammagard Liquid only group (n = 53) ³
Headache	3	
Hemolytic anemia	2	
Thrombosis	2	
Adrenocortical insufficiency	1	
Back injury	1	
Bronchitis	1	
Cervical dysplasia	1	
Chest Pain	0	1
Cholecystitis	0	1
Convulsion	0	1
Degenerative disc disease	1	
Gastroenteritis	1	
Leukoplakia of tongue	1	
Peptic ulcer disease	1	
Pneumonia	1	
Respiratory failure	1	
Seizure, grand mal	0	1
Seizure, petit mal	1	
Sinusitis	0	1
Status Epilepticus	1	

³ Note: In study 160601, 49 patients received Gammagard Liquid. In study 160603, 87 patients received Gammagard Liquid but 83 of these were subsequently transitioned to HyQvia. Thus, the Gammagard Liquid only population totals 53 patients.

Tonsillar hypertrophy	1	
Viral infection	1	
Totals	21	5

Additionally, there were 2 deaths in the total clinical safety database. One occurred in a patient who was enrolled in study 160601, but never received any study medication. (BLA Full Clinical Study Report 160601 p.129) Thus, the patient's death was unrelated to the study medication. The other death occurred during study 160902 and is described in detail below.

A detailed safety analysis of all 5 individual studies is provided below. Moreover, a detailed safety evaluation of rHuPH20 is addressed in Section 4B of this memo (Information suggesting a safety signal from other sources).

1. In study 160601, PID patients were initially administered Ig via the IV route every 3 to 4 weeks and were transitioned to Ig via the subcutaneous route given weekly, in order to study pharmacokinetics and tolerability. (Note: study 160601 did not involve the use of hyaluronidase, only the Ig component of HyQvia was given.) The study consisted of a prospective, open-label, non-controlled design. (BLA Risk Management Plan p29) Forty-nine patients were included in the safety analysis. Of these, 14 were 2 to 12 years of age, 4 were 12 to 16 years old, and 4 were >65 years of age. Thirty-eight patients were naïve to IgSC. During the IV portion there were 207 infusions, 226 AEs reported, and 85 were considered product related by the study investigator. For the SC portion, there were 2294 infusions, 634 AEs, and 150 were judged to be product related. Four (4) serious AEs were reported during the study; none were judged as product related.

The 4 serious AEs were sinusitis, cholecystitis, chest pain, and convulsion. The chest pain occurred in a 42year old female (Subject ---(b)(6)--) 2 days after her last Gammagard Liquid infusion. The chest pain was described as left sided and at the side of her Medi-port. She was evaluated and discharged the same day. (BLA Full Clinical Study Report 160601 p.131-2) The patient who experienced a convulsion was a 19 year old male (Subject -(b)(6)-). He received Gammagard Liquid on 4Feb2007 and had a seizure on 27Feb2008. He had a history of seizures and had been off anti-epileptic medications for approximately 1 year when the seizure occurred. Given the long latency between study medication and the AE, it is likely unrelated.

The proportion of infusions associated with AEs was greater for the IV subset than the SC subset (22.2% vs. 5.5%). The proportion of SC infusions with AEs reported declined as the study progressed, with 9.9%

in the initial SC part (Part 2 of the study). This declined to 7.8%, 3.5%, and 3.1% in subsequent phases of the study. These phases consisted of weekly SC infusions of Ig, with dose adjustment based on several different methods. This pattern of decreasing AE frequency was also true for injection site reactions during the SC phases of the study. The proportion of SC infusions which required a decrease in the infusion rate, interruption, or discontinuation for tolerability reasons was 0.2%. This finding means that IgSC was well tolerated by most patients and that patient tolerability improved over time.

2. Study 160603 was a prospective, open-label, non-controlled Phase III study of PID patients designed to study the efficacy, tolerability, and pharmacokinetic properties of HyQvia. (BLA Risk Management Plan p30-1) Specifically, the study aimed to evaluate the possibility of giving HyQvia at 3-4 week intervals, which is the indication that the sponsor is seeking. (This would be the identical schedule to Gammagard Liquid IV treatment, while most IgSC is given weekly or more frequently.) In the SC portion of the study, 24.5% (227 of 1129) of the infusions were temporally associated with AEs. There were 1085 AEs, including 11 serious. All 11 serious AEs were judged to be unrelated to the study medication. Of the non-serious AEs, 235 were local reactions and 839 were systemic. Six AEs were judged to be severe in intensity. PTs for the severe AEs included infusion site pain, infusion site swelling, genital edema, migraine, and oral pain. No subject developed neutralizing antibodies to rHuPH20 and there were no instances of hemolysis. (BLA Full Clinical Study Report: 160603, Synopsis p12)

Eighty-seven (87) subjects entered the study, 84 completed the IV portion, and 68 completed the entire study. The 16 patients who withdrew or discontinued during the SC portion cited the following reasons: 6 due to mild-moderate AEs, 5 withdrew without citing AEs (reasons included relocation, inconvenience and fear of needles in the abdomen), 1 due to increase in infections, 1 lost to follow-up, and 3 patients were transferred to “safety follow-up only.” Reasons for this transition were due to protocol issues (1 developed a positive anti-rHuPH20 antibody titer, 1 had medical issues and required a reduced Ig SC dose, 1 received an IV infusion instead of SC due to an infusion pump failure). (BLA Full Clinical Study Report: 160603 p69) As is typical for IgSC compared to IgIV, the rates for systemic reactions were lower for the SC infusions (HyQvia) than for the IV infusions (8.3% vs. 25.0%). Conversely, the rates for local reactions were higher for SC (HyQvia) infusions than for IV infusions (5.9% vs. 0.0%). (BLA Risk Management Plan p33) The most commonly reported AEs judged to be product-related for SC infusions were infusion site pain, infusion site erythema, infusion site discomfort, headache, infusion site pruritis, infusions site edema, and infusion site

swelling. All 7 events are labeled for Gammagard Liquid and appear in Section 6 of the draft label for HyQvia.

One of the safety concerns with HyQvia is the long-term effects, including local, systemic, and immune-mediated effects. It is known that anti-rHuPH20 antibodies cross react with male reproductive tissue and bind to enteric plexus neurons. A total of 41 subjects received HyQvia for greater than 1 year as part of Study 160603. There were no chronic local effects observed. (BLA Clinical Overview p18) However, follow-up time may have been insufficient to observe chronic effects, particularly on the GI and reproductive systems. In addition, the trial was not designed to evaluate effects on fertility.

Two (2) patients in Study 160603 experienced a thromboembolic event (TEE). Subject --(b)(6)- was a 66 year old male who last received HyQvia on 21Dec2009. He experienced a fatal myocardial infarction on ----(b)(6)- -----, nearly 4 months after last receiving HyQvia. In the time between the last dose of HyQvia and his death, the patient had a back injury, underwent spinal surgery, and had received a blood transfusion and Gamunex. He had a history of hypertension and hypercholesterolemia. Given the time between the last dose of study medication and death, the AE of MI was judged to be unrelated by study investigators.

Subject --(b)(6)--, a 19 year old male, experienced a right subclavian vein thrombosis during Study 160603. The subject received HyQvia on 30Nov2009. On 13Dec2009, 13 days after receiving HyQvia, the patient developed a swollen and “reddish blue” right hand. Forty days previously, the patient had a non-functioning venous access device replaced in the right UE. A right subclavian thrombosis was confirmed by ultrasound. The subject had a history of hyperlipidemia and a positive family history of thrombosis (no details provided). Study investigators judged the event “unrelated” to the study medication, although the time frame of 13 days is plausible for a venous event. However, an in-dwelling catheter or port is a clear risk factor for venous thrombosis.

Other noteworthy serious AEs included the 3 terms indicating seizures and 1 of “respiratory failure.” Subject-(b)(6)- was a 37 year old female with a history of Schwannoma and surgical excision in 2004. She had a seizure disorder and was on medication. On 6Oct2009, she received Gammagard Liquid. On 13Oct2009, 7 days after treatment, she experienced a grand mal seizure. One report notes the patient may have had concomitant pneumonia. (BLA Full Clinical Study Report 160603, p1334-7) This same patient also experienced the AE of petit mal seizure on 10Jan2010. On the day of her infusion of HyQvia, she experienced an aura, right sided weakness, and tachycardia. She was admitted to a hospital for observation. A CT was negative for acute changes and an ECG showed

no ST-T changes. The patient had a history of Todd's paralysis, so the right sided weaknesses could have been a manifestation of her seizure disorder (rather than a TEE). (BLA Full Clinical Study Report 160603, p1354-6)

Patient -----(b)(6)----- was a 15 year old female with a known seizure disorder who received HyQvia on 29Oct2009. On 21Nov2009, 23 days after treatment, she was hospitalized with status epilepticus and respiratory failure. (BLA Full Clinical Study Report 160603, p1339-40) Given the patient's history and the latency, the seizure is very unlikely to be related to HyQvia.

3. Study 160902 was a prospective, open-label, non-controlled study in PID patients, designed to evaluate long term tolerability and safety of HyQvia. This is an extension of study 160603 – subjects completing that study could enroll in 160902 and continue for up to 2 years. Sixty-six subjects enrolled. Six were discontinued when their study site closed and one subject died. The subject was a 57 year old female with a complicated medical history. She died 1 week after her 4th infusion due to “multiple drug interactions.” (BLA Risk Management Plan p33) Review of the MedWatch reports concerning this patient confirms that the patient was taking 29 regular or prn medications and had significant morbidities, including primary ID, asthma, gastritis, hx of bleeding ulcer, aortic aneurysm, syncope, depression, hypothyroidism, drug dependence, and type 2 DM. The medical examiner performed an autopsy and concluded the patient's death was due to “mixed drug toxicity” with the possible contributing factors of DM, malnutrition, and hypothyroidism. Her death was judged by the investigator to be unrelated to the study medications. (AERS ISR Information Report for ISR# 7500103-9)

There were no imbalances in the rate of adverse events in this long term follow up study consisting of 66 people.

4. Study 170901 was the only prospective, randomized, double-blind, controlled study in clinical development program and enrolled healthy volunteers to assess safety, tolerability, and maximal flow rate of IgSC with or without rHuPH20. This study is important because it assesses product safety in individuals who were naïve to immune globulin and did not have the baseline confounding associated with the preexisting conditions in the product's indicated population. Baseline evaluation consisted of CBC, Chemistry panel (---(b)(4)---), testing for Hepatitis B and C and HIV, serum IgA level, and anti-rHuPH20 antibodies. Lab evaluation at infusion visits included Coombs testing, haptoglobin, LDH, reticulocyte count, and free hemoglobin level. Twelve patients were enrolled but the study was terminated early due to the serious AE of hemolytic anemia in 2 patients. These patients experienced flu-like illness

and elevations of LFTs. (BLA Full Clinical Study Report: 170901 Part4 p74)

Subject -(b)(6)- was a previously healthy 32 year old AA male, blood type A+, who developed a flu-like illness 2 days after receiving IgSC. He was diagnosed with hemolytic anemia and lymphopenia 6 days after receiving IgSC. The subject's hemoglobin dropped from a baseline of 15.3 to 11.0 g/dL. The subject had a negative Coombs test at the start of the study and was Coombs positive when he presented with the flu-like illness. The subject received IgSC 3 times over the 20 days prior to experiencing the AEs. His total IgSC dose was 1.2g/kg. Product quality investigations did not reveal any product issues. (BLA Full Clinical Study Report: 170901 Part4 p152-9)

Subject -(b)(6)- was a previously healthy 47 year old white male, blood type A, who developed a flu-like illness (myalgia, chills, fever, dizziness) 8 days after his 4th dose of study medication. The subject's hemoglobin dropped from 14.5 at baseline to 10.2. The subject had a negative Coombs test at the start of the study and was Coombs positive when tested 7 days before the flu-like illness. Eluate from the patient's RBCs revealed anti-A antibody. He also had elevated LFTs, amylase, and lipase. He received a total dose of 1.8g/kg of IgSC. Product quality investigations did not reveal any product issues. (BLA Full Clinical Study Report: 170901 Part4 p159-70)

In addition to these 2 patients, 3 other study patients reported a flu-like illness and 5 additional patients had increased titers to influenza virus. So, 10 of 12 patients in the study had evidence of influenza infection. The study was conducted in Kansas City between 22Sep2009 and 30Oct2009 (when enrollment was halted). There was a high incidence of 2009 H1N1 influenza in the area during this time. (BLA Full Clinical Study Report: 170901 Part4 p83) The trial was terminated on 2Nov2009.

The sponsor concluded the hemolysis was related to influenza A (based on antibody titers) rather than the study medication. Patients had elevated titers to several influenza viruses, including A/Brisbane, 2009-H1N1, B/Brisbane, and H3N2 A/Uruguay. A consultant concluded that these responses were likely heterotypic, since 2009-H1N1 was the predominant virus in circulation at the time of the study. (BLA --(b)(4)-- April2012, --(b)(4)-- July2012). In addition, both --(b)(4)----- and the sponsor conclude that the rise in antibody titers was unlikely to be due to the passive transfer of antibodies in IgSC (BLA Virology Serology Investigation p1-10) The sponsor notes that no other cases of hemolysis have been reported in conjunction with this lot, which was used both in this study and distributed for general use.

In conclusion, hemolysis is a known and labeled event for Gammagard Liquid, but HyQvia is not suspected as being the direct cause of these hemolysis events. Supporting evidence includes the lab values not typically seen in Ig-associated hemolysis (elevated pancreatic and LFTs), clinical and antibody titer evidence of a plausible alternative etiology (influenza), and the absence of hemolytic events in other HyQvia studies and in patients who received the same lot of Gammagard Liquid used in Study 160603.

The duration and maximum volume of infusions were similar between both the rHuPH20 group and the buffer control group. However, subjects in the rHuPH20 group had fewer site reactions, as well as site reactions of small size and shorter duration. (BLA Risk Management Plan p36-7)

5. Study 161001 was a Phase 1, prospective, randomized, placebo controlled study to assess the effectiveness of rHuPH20 in facilitating IgSC infusion. (BLA Risk Management Plan p37). Fifty-three subjects were enrolled and 51 completed the study. Of the 2 subjects who did not complete the study, one was lost to follow-up and the other withdrew due to an AE of moderate hypotension (following rHuPH20/Lactated Ringer's infusion. The subject did not receive any Ig.).

The 53 subjects reported a total of 363 AEs, 337 (92.8%) of which were judged to be product related. All were non-serious and there were no deaths in the study. AEs rated to be severe in intensity accounted for 5.2% of events (19/337). (BLA Risk Management Plan p38-9)

b. Safety concerns

This section reviews the pharmacovigilance plan provided by the sponsor. The safety specification is based upon data on the clinical safety of HyQvia is based on the studies described above. OBE's evaluation of the PVP is found in Section 6 (Integrated Risk Assessment).

While HyQvia is based upon 2 licensed products with well described safety profiles, there is no clinical experience with the combination product beyond the above studies, as HyQvia is not yet licensed in any country.

i. Important identified safety issues

Important identified safety issues identified previously with Gammagard Liquid and common to the IG class include allergic/hypersensitivity reactions, local reactions, altered immune response (including reduced efficacy of live virus vaccines, interference with serologic testing (due to the passive transfer of antibodies) and positive transfer of erythrocyte antigens (leading to a positive Coombs test)), aseptic meningitis syndrome, and transfusion related acute lung injury (TRALI). The sponsor proposes to address these risks through routine pharmacovigilance. (BLA PVP p41-3)

ii. Important potential safety issues

Important potential safety issues include hemolysis, thrombotic events, renal dysfunction/failure, (risk of) transmittable infectious agents, and localized infection. All of these important potential issues (except localized infection) are common to the IgIV class and are labeled for all IgIVs, including Gammagard Liquid, the IgIV contained in HyQvia. Localized infection is a risk with any injectable product. The sponsor proposes to address these risks through routine and “additional” pharmacovigilance. Specifically, the sponsor proposes to submit all hemolysis and thrombotic event reports as 15 day (expedited) reports.

iii. Important missing information

Patient groups with important missing information include pregnant and lactating women, neonates and infants <2 years old, and geriatric patients >65 years of age. There were 22 pediatric subjects 2 to 16 years old in the clinical trials and the safety and efficacy of HyQvia were similar to adult patients according to the proposed package insert. Similarly, 7 subjects >65 years were involved in the clinical trials and no differences in safety or efficacy were detected. Routine pharmacovigilance for these patient groups with currently limited or missing information is proposed by the sponsor.

One area of important missing information (not addressed by the sponsor in the PVP) is the potential for adverse events due to the generation of auto-antibodies (against human PH20) due to the chronic use of HyQvia. These adverse effects could be local or systemic. While no chronic local adverse events were seen in the trials (in which 41 patients used HyQvia for >1 year), it is possible that lifelong use could lead to lasting changes in the skin or subcutaneous tissues, particularly at the sites of injection. In addition, anti-rHuPH20 antibodies were found in many patients receiving HyQvia. These antibodies could alter neuronal migration or lead to male infertility by binding to male reproductive tissues. The extent of these effects in humans and whether these could be more problematic in pediatric patients or those exposed *in utero* is unknown. Additional information about this issue can be found below in section 4b.

c. Sponsor’s proposed actions and timelines

i. Enhanced pharmacovigilance activities proposed by the sponsor

The sponsor proposes to submit all hemolysis and thrombotic events as 15-day expedited reports.

ii. Review of post-marketing studies

There are no proposed PMRs, nor PMCs.

4. Review of other information from the managed review process

a. Pertinent positive information suggesting a safety signal from the clinical or statistical reviewer

None

b. Information suggesting a safety signal from other sources

A theoretical risk of HyQvia is damage to enteric plexus neurons and/or male infertility, due to anti-PH20 antibody generation. This issue was discussed extensively at the FDA-EMA-HC Blood Cluster Teleconference on 4May2012 (FDA-EMA-HC Blood Cluster Teleconference meeting minutes). Details are provided below but a few key points from this discussion were as follows:

- The long term effects of HyQvia, including local, systemic, and immune-mediated effects, are unclear.
- Long-term data on the effects of HyQvia are missing.
- The immunogenicity of rHuPH20 used in combination with IgSC is unexpectedly high.
- An effect of anti-rHuPH20 antibodies on fertility cannot be excluded. This is a particularly sensitive issue for use in a non-consenting (pediatric) population, where the implications may be lifelong.

The use of rHuPH20 in HyQvia differs from the currently licensed hyaluronidase, Hylenex, in several important ways. First, Hylenex is used for single or short-term applications (e.g., to facilitate the infusion of contrast media when IV access cannot be obtained) whereas HyQvia is designed for life-long use at 3-4 week intervals. In addition, the doses of rHuPH20 in HyQvia are 17.5 fold higher (for a 70kg adult) than the indicated dose for Hylenex. Furthermore, there are widely used and well-tolerated therapeutic alternatives to HyQvia (IgIV and IgSC), so this alters the risk tolerance for potentially serious adverse events. The main advantage of HyQvia over IgSC is that HyQvia can be given at 3-4 week intervals, instead of weekly. This may offer increased convenience to the patient and increased quality of life.

The EMA presented information -----
----- (b)(3) -----

----- Dr. Jennifer Reed of FDA presented information that 50% of patients in clinical trials were positive for anti-rHuPH20 antibodies at some point and that 1 in 10 were persistently positive. However, there was no evidence that the antibodies were neutralizing.

The neurons of the enteric plexus and the testes are the potential targets for anti-rHuPH20 antibodies, as these tissues express PH20. Neurons have been found to secrete enzymes (including hyaluronidase) which modify the extracellular matrix (ECM) *in vitro*. Furthermore, the ECM plays a role in neural stem cell proliferation and differentiation. (FDA-EMA-HC Blood Cluster Teleconference meeting minutes) ----- (b)(3)/(b)(4) -----, since anti-rHuPH20 antibodies cross-react with male reproductive tissue and fertility impairment has been shown in at least 1 animal model (guinea pig).

(FDA-EMA-HC Blood Cluster Teleconference meeting minutes) Thus, these antibodies could potentially damage the developing GI system and/or male reproductive tissues, especially if a developing fetus or young child very exposed.

5. Post-licensure safety review

N/A. HyQvia is not currently licensed in any country.

6. Integrated Risk Assessment

a. Description of important safety issues identified by the reviewer from any source that do not trigger a PMR or REMS.

The most important potential safety issue is possible damage to the enteric plexus and/or male reproductive tissues due to the generation of auto-antibodies directed against PH20 secondary to chronic use of the rHuPH20 component of HyQvia.

The FDA has expressed these concerns to the sponsor and the sponsor has outlined a strategy for a series of pre-clinical studies to provide additional safety data. In addition, the sponsor has requested a face-to-face meeting with the FDA (which may take place in early July 2012).

According to the sponsor, these preclinical studies would be performed “in a sequential manner, where the outcome of the first studies would inform the design of any additional studies.” (BLA Baxter HyQvia Studies Proposal, received by FDA 29May2012 p5) Topics of the proposed study include characterization of anti-rHuPH20 antibodies by comparing the antibodies (if present) in normal individuals and those who receive IgIV to the antibodies present in patients treated with HyQvia and assessing the binding of rHuPH20 antibodies to the neuronal plexus and male reproductive tissues. “Pending the results of the Stage 1 activities [described in the preceding sentence], Baxter will initiate further dialogue with FDA before providing a definitive proposal for future preclinical studies.” (BLA Baxter HyQvia Studies Proposal, received by FDA 29May2012 p10)

It is not possible to predict how the results of these preclinical studies will affect the approval of HyQvia and any subsequent post-marketing studies at this time. If concerns regarding the potential adverse effect of anti-rHuPH20 antibodies remain following pre-clinical studies (and HyQvia is approved), this will need to be addressed in the Pharmacovigilance Plan. In addition, post-marketing studies may be needed.

A second important safety issue is hemolysis, as seen in 2 patients in study 170901 (see section 3a. Clinical Safety Database, above). Hemolysis is a known adverse event following IgIV. In addition, 2009- H1N1 influenza viral infection may have been a contributing factor in these 2 patients. Hemolysis was not observed in other patients receiving HyQvia as part of a clinical trial, nor was hemolysis reported with the lot of Gammagard Liquid used in the clinical trial. (This lot was also distributed for general use.) The sponsor has proposed to

submit all reports of hemolysis as 15-day (expedited) adverse event reports, and this plan is acceptable.

b. Description of any signals identified by the reviewer from any source that trigger a REMS or PMR (in the reviewer's opinion)

None at this time. The results of the proposed pre-clinical studies regarding the potential adverse effect of anti-rHuPH20 antibodies could potentially indicate the need for a PMR or REMS in the future. For example, if anti-rHuPH20 antibodies are found to be damaging to male reproductive tissue, HyQvia use could be restricted to certain patient populations (i.e., it might be contraindicated in pregnant women and male children).

7. Recommendations

Currently, there is insufficient information to establish the safety of long-term HyQvia use. Safety issues which need further study include the potential for anti-rHuPH20 antibodies to bind to enteric plexus neurons, causing subsequent changes in neuronal migration or neuronal function. In addition, anti-rHuPH20 antibodies are known to react with male reproductive tissue and infertility was observed in a guinea pig animal model. Further study is needed to establish what effect (if any) chronic HyQvia use has on fertility. This has significant implications, given the potential for lifelong use, use in pediatric patients, and the potential for *in utero* exposure.

CBER plans to issue a complete response letter. OBE recommends that the sponsor update the safety specification and Pharmacovigilance Plan after the sponsor's proposed new studies investigating the potential risk of anti-rHuPH20 antibodies have been completed. OBE will review the updated PVP and safety specification upon submission to determine the need for future post-marketing studies or a REMS.