

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

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| From: | <p>Scott K. Winiacki, MD Medical Officer, Pharmacovigilance Branch Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE)</p> <p style="text-align: center;">APPROVED <i>By Scott K. Winiacki, M.D. at 1:01 pm, Apr 18, 2014</i></p> |
| Through: | <p>Craig Zinderman, MD, MPH Acting Chief, Pharmacovigilance Branch</p> <p style="text-align: center;">APPROVED <i>By Craig Zinderman, MD, MPH at 2:57 pm, Aug 18, 2014</i></p> |
| | <p>Manette Nui, MD Acting Director, DE OBE</p> |
| BLA/Supplement Number | 125402/0 |
| Subject: | Addendum to Pharmacovigilance Memorandum |
| Applicant: | Baxter Healthcare Corporation, Baxter Bioscience |
| Product: | HyQvia Immune Globulin Infusion (Human), 10% with Recombinant Human Hyaluronidase |
| Proposed Indication: | Primary immune deficiency (PID) associated with defects in humoral immunity |
| Submission Date: | Response to Complete Response received 12Dec2013 |
| PVP Submission Date (if applicable): | 26Nov2013 (version 2, dated 21Nov2013) |
| Action Due Date: | 13Jun2014 |

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 (PVP), 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 hyaluron 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

| Action | Date |
|---------------------|-----------|
| Original submission | 20Jun2011 |
| PVP memo | 8Aug2012 |
| CR letter issued | 27Jul2012 |
| Resubmission | 12Dec2013 |
| Action Due Date | 13Jun2014 |

i. Prior licensure in other nations

HyQvia was licensed in the European Union (EU), via the centralized procedure, on 16May2013. The product was first launched in Germany, on 21Jul2013. (PVP, version 2, 21Nov2013, p6)

1. Summary of indications and usage

HyQvia is “indicated for the treatment of humoral immune defects in adult patients (≥ 16 years) with Primary Immunodeficiency.” (Proposed HyQvia USPI, Indications and Usage section)

Reviewer Comment: The age range is a change from the original submission, which did not specify an age range.

2. Major postmarketing safety findings

As of 21Nov2013, the sponsor had received four (4) post-marketing adverse event reports. (PVP, v2, p41)

Reviewer Comment: Given that the first product launch occurred in late July2013, only 4 months elapsed between launch and the preparation of the PVP. Therefore, the small number of reports is expected and of limited utility in interpreting the safety profile of HyQvia.

ii. CBER Complete Response letters

A Complete Response letter was issued on 27July2012. The CR was based upon concerns regarding the generation of anti-hyaluronidase antibodies (anti-PH20). Specifically, the FDA requested additional information regarding the possible toxicity of lifetime exposure to anti-PH20 antibodies, the possible toxicity of anti-PH20 antibodies to the fetus or neonates following transplacental exposure, the possible toxicity to pediatric patients, and the possible effect of anti-PH20 on male and female fertility. (CR letter, 27Jul2013)

b. Objectives/Scope of the 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.

This addendum will address changes made to the PVP following the CR letter of 27Jul2013 and submitted as version 2. For a review of the clinical studies, please refer to the Pharmacovigilance Memorandum of 8Aug2012. (Available in the CBER EDR)

2. **Materials reviewed** – Materials reviewed in support of this assessment include:

a. Routine items:

- i. Pharmacovigilance Plan, versions 1 and 2
- ii. Pertinent sections of the licensing application selected by the reviewer

Clinical Overview

Full Clinical Study Report: 1606093

Full Clinical Study Report: 170901

Proposed HyQvia USPI

iii. Postlicensure Safety Data

1. *AERS*

Since HyQvia is a combination product of 2 licensed products (Gammagard Liquid and hyaluronidase), adverse events for these 2 products were reviewed in the first pharmacovigilance memorandum. Please refer to

this document for a summary of the adverse event profiles for these 2 products.

It should be noted that the hyaluronidase in HyQvia is different from that in licensed products and that HyQvia would be used on a chronic basis, in contrast to one-time exposures for radiologic studies, etc.

- iv. Input from CBER reviewers in other disciplines
HyQvia was discussed at the OBE/OBRR SAM on 15Jan2014 and at the CBER Blood meeting on 11Feb2014. At each meeting, updated information on HyQvia was presented by Jen Reed, PhD., of OBRR. Concerns continue to focus around the generation of anti-PH20 antibodies by patients receiving HyQvia. These antibodies have been observed to bind to normal human tissue, although no adverse events associated with these antibodies were observed during the clinical trials.

In response to the CR letter, the sponsor conducted a 6 month study in a mouse model. Dr. Reed did not feel this qualified as a “lifetime” study, as requested by CBER. In addition, the sponsor conducted a second study in rabbits to analyze the effects of anti-PH20 on fertility, embryo-fetal development, and juvenile development. While no adverse effects were found, this study does not address the possible effects of anti-PH20 on neural or glial cells or in the setting of neuronal damage (where PH20 is known to be expressed in humans).

Since the risk of long-term effects is uncertain and studying these effects could take years (if possible at all in humans), the plan following the CBER Blood meeting was to consult two (2) outside experts in hyaluronidase research. These experts will address the role PH20 in neuronal tissue and the possible long term implications for human health.

- b. Other items**
 - i. Information received under MOU from foreign regulatory or public health agencies
EMA will share data with FDA when it becomes available.
 - ii. Advisory Committee reviews
None to date.
 - iii. International postmarketing experience with the same product
The product was initially launched in July 2013. Given this short time frame and the minimal number of reports received to date, no conclusions can be drawn from post-marketing experience in other countries.

3. Pharmacovigilance Plan Review

a. Clinical Safety Database

For a review of clinical studies, please refer to the PV memo of 8Aug2012.

The sponsor has revised the safety issues identified for HyQvia since the first version of the PVP. The changes are described below:

| Safety Concern | Comment |
|--|---|
| Allergic/hypersensitivity responses including anaphylactic reactions and IgA deficiency | Revised to: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency |
| Local reactions | Revised to: Infusion site reactions (including Discomfort/Pain, Erythema, Swelling/Edema, Pruritus, Infusion site mass, Nodule, Infusion site warmth, Infusion site hematoma, and Infusion site hemorrhage) |
| Altered immune response <ul style="list-style-type: none"> • Reduced efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella • Interference with serological testing after infusion on immunoglobulin • Positive transfer of antibodies | Revised to: Altered immune response: <ul style="list-style-type: none"> • Reduced efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella • Interference with serological testing after infusion of immunoglobulin |
| Transfusion related acute lung injury (TRALI) | Recharacterized as an Important Potential Risk (previously an Important Identified Risk) as it has only been known to occur with intravenous IgG treatment. |
| Hemolysis | Recharacterized as an Important Identified Risk to align with global regulatory assessments and revised to: Hemolysis/Hemolytic anemia |
| Thrombotic events | Recharacterized as an Important Identified Risk to align with global regulatory assessments and revised to: Thromboembolic events |
| Localized infection | Revised to: Spread of localized infection |
| Drug administration error: Incorrect sequence of administration of vials | Added as an Important Potential Risk |
| Lack of information in pregnant and lactating women | Revised to: Lack of clinical data on safety in pregnant and lactating women |

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| Limited information in neonates or infants < 2 years old | Revised to: Lack of clinical data on safety in neonates or infants <2 years old |
| Limited clinical data on long-term treatment in patients under the age of 16 years | Added as an item of Missing Information |
| Limited information in geriatric patients over age 65 | Revised to: Limited information on safety in geriatric populations |
| Lack of clinical data on the potential consequence of antibody development against Recombinant Human Hyaluronidase of HyQvia | Added as an item of Missing Information |
| Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against Recombinant Human Hyaluronidase of HyQvia | Added as an item of Missing Information |
| Limited clinical data on patients with serum creatinine levels greater than 1.5 times the upper limit of normal for age and gender | Added as an item of Missing Information |

(PVP, v2, p36)

The “ongoing safety issues” are summarized below (Table 2.1-1 from the PVP, v2):

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|----------------------------|--|
| Identified Risks | Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency |
| | Altered immune response: <ul style="list-style-type: none"> • 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 (including discomfort/pain, erythema, swelling/edema, pruritus, infusion site mass, nodule, infusion site warmth, infusion site hematoma, and infusion site hemorrhage) |
| | Thromboembolic events |
| | Hemolysis/Hemolytic anemia |
| | Aseptic meningitis syndrome (AMS) |
| | Potential Risks |
| | Spread of localized infection |
| | Renal dysfunction/failure |
| | Transfusion-related acute lung injury (TRALI) |
| | Drug administration error: incorrect sequence of administration of products |
| Missing Information | Lack of clinical data on safety in pregnant and lactating women |
| | Lack of clinical data on safety in neonates or infants <2 years old |
| | Limited clinical data on long-term treatment in patients under the age of 16 years |

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| | Limited information on safety in geriatric populations |
| | Lack of clinical data on the potential consequence of antibody development against Recombinant Human Hyaluronidase of HyQvia |
| | Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against Recombinant Human Hyaluronidase of HyQvia |
| | Limited clinical data on patients with serum creatinine levels greater than 1.5 times the upper limit of normal for age and gender |

b. Safety concerns

i. Important identified safety issues

There are six (6) important identified safety issues. Allergic/hypersensitivity responses, altered immune responses, hemolysis, thromboembolic events, and aseptic meningitis are adverse reactions common to the immune globulin class. While systemic reactions are less common with subcutaneously administered Ig (compared to IVIg), they are known to occur and are already described in the PI for Gammagard Liquid. (Gammagard Liquid PI, 9/2013 ed., see “Warnings and Precautions” and “Drug Interactions”) Infusion site reactions are the most common adverse event after subcutaneous Ig administration. These are well described in the Gammagard Liquid PI.

Since Version 1 of the PVP, hemolysis and thromboembolic events have been added to the “important identified risks” category. Two patients had a TEE in Study 160603, although only one was potentially related. (Full Clinical Study Report: 1606093, p1363) Two patients had hemolysis after HyQvia in Study 170901, which was conducted in healthy volunteers. (Full Clinical Study Report: 170901, Part4, p152-70)

Reviewer Comment: Thromboembolic events and hemolysis have been reported in patients receiving IgSC and in the HyQvia trials. Inclusion of these two events as “important identified risks” is appropriate.

ii. Important potential safety issues

The PVP lists five (5) potential risks. Three (3) of these risks are common to Ig products: transmittable infectious agents, renal dysfunction/failure, and transfusion-related acute lung injury (TRALI). “Spread of localized infection” is a potential risk, if HyQvia were administered through an infected site. The proposed labeling contains instructions to avoid “areas that are inflamed or infected.” (PVP, v2, p96) The final potential risk is “Drug administration error: incorrect sequence of administration of products.” That is, the patient could

administer the immune globulin first, followed by the hyaluronidase. The possible result would be a non-serious but larger or more intense local site reaction (pain, swelling, etc.). The sponsor suggests that if this mistake were made repeatedly, the patient could receive less Ig (due to site reaction or increased infusion pressures resulting in pump shut off), leading to increased risk for infection. (PVP, v2, p53-4) The proposed labeling and the “Information for Patients” section provides clear instructions with illustrations on how to administer HyQvia. The 2 bottles are of different size and are labeled “HY” and “IG” to minimize any confusion. (PVP, v2, p115-21)

Since version 1 of the PVP, TRALI was changed from an identified risk to a potential risk. The sponsor states that TRALI has been reported only with IV administration of Ig. A search of FAERS on 14Mar2014 using a comprehensive list of Ig products and the Preferred Term “Transfusion-related Acute Lung Injury” found 18 cases. Seventeen of these were confirmed to be IV administration. One case did not specify a route, but it was for a product approved only for IV administration.

The risk of “incorrect sequence of administration” has also been added to the potential risks since version 1 of the PVP. While this type of error is always possible in a combination product packaged in 2 vials, the risk can be minimized through clear instructions and distinct labeling.

Reviewer Comment: TRALI has been moved from an identified risk to a potential risk in version 2 of the PVP. A search of FAERS did not find any documented cases of TRALI following SC administration of Ig. Therefore, this change is appropriate. While sequence of administration errors are possible, the sponsor has provided clear instructions, illustrations, and prominent labels on the vials to minimize the chance of this error.

iii. Important missing information

Four (4) additional categories of “important missing information” have been added since version 1 of the PVP. In addition to lack of information in pregnant and lactating women, children < 2 years, and patients > 65 years, “limited clinical data on long-term treatment in patients under the age of 16 years” has been added. (PVP, v2, p37) A total of 36 patients < 18 years have participated in the HyQvia clinical trials. (PVP, v2, p32) Similarly, “limited clinical data on patients with serum creatinine levels greater than 1.5 times the upper limit of

normal for age and gender” has been added. This category of patients was excluded from the clinical trials. (PVP, v2, p34)

The last two categories of missing information concern the development of anti-hyaluronidase antibodies following exposure to HyQvia. The missing information is described as “limited clinical data on the potential for long-term local and systemic reactions” to these antibodies and “limited clinical data on the potential consequence of antibody development.” (PVP, v2, p38)

Reviewer Comment: The possible long-term effects of anti-PH20 antibodies are the most important safety issue with HyQvia. It is known that these antibodies are generated in some patients and that anti-PH20 antibodies can bind human tissue. It is unknown if these antibodies would cause adverse effects, particularly during specific times of PH20 expression, such as fetal development and during neuronal injury and remyelination.

- c. Sponsor’s proposed actions and timelines
 - i. Enhanced pharmacovigilance activities proposed by sponsor
For thromboembolic events, the sponsor proposes three enhanced activities. First, TEEs will be reported as expedited events. The sponsor will conduct an evaluation of TEE reports and comment on these reports in the product periodic reports. Finally, the sponsor has proposed a “Thromboembolic Event Questionnaire.” This questionnaire is designed to identify risk factors for TEE such as cardiac conditions, prior TEEs, malignancies, trauma, immobilization, inflammatory disorders, medications, hypercoagulable states, and other risk factors. (PVP, v2, p376-8) Although not described in the PVP, this tool would presumably be administered to any reporter of a TEE event, in an effort to obtain important information.

For the “lack of clinical data on the safety in pregnant and lactating women,” the sponsor proposes a pregnancy registry. There is a statement in the proposed labeling that exposed pregnant women should be encouraged to enroll in the pregnancy registry. (PVP, v2, p102) However, an outline or protocol has not been submitted.

Reviewer Comment: Pregnancy registries are a common method to evaluate if a therapeutic has any adverse effect on pregnant women or the fetus. Further assessment of the proposed study is not possible since no details have been provided.

For the “limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development” against PH20, the sponsor has also designed a questionnaire to better document the signs and symptoms of a reported allergic reaction. The form also documents treatment given and laboratory tests performed. (PVP, v2, p379-81) In addition, the sponsor proposes to comment on the safety data related to immunological events reports in the HyQvia periodic reports. Finally, the sponsor has proposed a post-authorization safety surveillance (PASS) to study any long-term local and systemic effects which might result from anti-PH20 antibodies. Again, the sponsor has not provided a description, outline, or protocol for this study.

Reviewer Comment: The sponsor does not state how the questionnaire would be administered and clarification would be useful.

Given the lack of a description or protocol, further assessment of the PASS is difficult. However, for such a study to be effective, a cohort of patients with anti-PH20 antibodies would need to be identified and followed for a lengthy period, potentially years, to detect possible effects. In addition, since PH20 expression occurs during specific times such as neuronal injury and remyelination, these patients would require frequent follow-up to detect such events and follow their recovery. Any study requiring long and frequent follow up is difficult and tends to lack power, as many subjects are lost over time. Given the long time frame and the possibility that effects might only be seen following CNS injury or demyelination, the study will be extremely difficult to conduct. If not designed appropriately, it will fail to detect long term effects. If designed well, it may be exceedingly costly and difficult to conduct the follow up of a significant number of patients.

- ii. Review of Postmarketing Study proposal or protocol synopsis
As stated above, the sponsor has proposed two (2) postmarketing studies: a pregnancy registry and a PASS to examine any potential long term local and systemic adverse events which might result from anti-PH20 antibodies. As stated above, the study may be very challenging to design and costly to conduct. The sponsor has not yet provided a protocol (or any details) on either study. Therefore, further assessment is not possible at this time.

4. Review of other information from the Managed Review process

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

Please see section 2.A.iv. above for information regarding the potential for adverse events resulting from anti-PH20 antibodies.

- b. Sections of the licensing application selected by the OBE/DE reviewer

While it is known that some patients develop anti-PH20 antibodies and that these antibodies can bind human tissue, what effect (if any) this might have over time is unknown. In order to better understand the degree of risk, two experts in hyaluronidase research were recruited as Special Government Employees (SGEs) to provide insight into the latest research and how this knowledge might contribute to estimating the risk of long term effects from anti-PH20 antibodies. The questions the SGEs were asked to respond to were:

- Q1. Please address current understanding of PH20 expression in neurons, glia, and their precursors in humans, and in other mammalian species (mice, rabbits, monkeys). Please describe developmental observations and role of PH20 post-injury.
- Q2. Please elucidate the current understanding of how PH20 contributes to neuronal homeostasis and function, including roles in oligodendrocyte maturation and remyelination in CNS lesions.
- Q3. Please comment on whether adverse events could result from chronic exposure to elevated anti-PH20 antibodies in humans. What preclinical studies might be useful in evaluating potential adverse events associated with anti-PH20 exposure?

SGE #1 responded that there are no studies which show PH20 as being expressed in normal human adult CNS tissue. However, there are several researchers who have detected PH20 expression in -----

----- (b)(4) -----

----- Based on this and the existence of the blood-brain barrier, the SGE concluded "I would consider it highly unlikely that PH20 antibodies would influence the nervous system, unless there were an inflammatory neurological condition where B cells accumulated in the brain (e.g. in lesions, meninges or other brain connective tissues spaces as occurs in progressive forms of multiple sclerosis)." (Confidential communication from SGE #1 to FDA, 20Feb2014) The SGE did express that fertility could be affected by anti-PH20 antibodies. "Given that the highest levels of PH20 are found in testes, it is possible that PH20 antibodies (assuming they had neutralizing activity) could lead to at least transient male infertility." (Confidential communication from SGE #1 to FDA,

20Feb2014) However, this might only be an issue in the context of testicular inflammation, where the antibodies could cross into the testes.

SGE #2 has not yet responded to the questions posed by FDA.

5. Postlicensure Safety Review

The product was initially launched in July 2013. Given this short time frame and the minimal number of reports received to date, no conclusions can be drawn from post-marketing experience in other countries. The EMA and FDA regularly discuss safety findings at the CBER-EMA-Health Canada Blood Cluster meeting. HyQvia has been discussed at previous meetings and the EMA has agreed to share any safety signals for findings for HyQvia.

HyQvia was discussed on the FDA-EMA Pharmacovigilance teleconference on 2April2014. EMA conducted a search for products containing the ingredient “hyaluronidase” and the text string “antibod” and “cross-react.” -----

----- (b)(3) -----

----- (EMA/FDA Pharmacovigilance teleconference briefing materials, 2April2014)

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

There is a lack of data regarding the possible effects of HyQvia during pregnancy. The sponsor has proposed a pregnancy registry. While this is a typical approach, further assessment is not possible until a protocol is submitted.

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

There is concern that anti-PH20 antibodies which develop in some HyQvia recipients pose a risk to male fertility and to CNS injury repair. This is a potential risk, since no adverse events were seen in the clinical trials. However, it is possible that the adverse effects would only be seen after a long duration or under special conditions, such as CNS injury. While labeling could address some of this risk, CNS injury or demyelination is unpredictable. (That is, we do not know prospectively who might have a stroke, traumatic brain injury, or MS). The sponsor has proposed a PASS to assess long term effects. However, since there is no additional description of how this study might be conducted, further assessment is not possible at this time.

7. Outstanding Sources of Data Requiring Review

a. Response by SGE #2

The response to FDA's questions by SGE #2 is still pending and may inform the degree of risk anti-rHuPH20 antibodies pose in the setting of CNS injury.

b. AE reports from the sponsor

FDA has requested all AE reports for HyQvia from the sponsor. These will be reviewed for evidence of antibody development and resulting AEs (if any).

c. AE reports from EMA

On the PV teleconference on 2April2014, FDA requested EMA to forward copies of all AE reports received for HyQvia. These will be reviewed to assess any safety issues, particularly with respect to AEs following development of anti-rHuPH20 antibodies.

8. Recommendations

The sponsor has proposed several activities beyond routine pharmacovigilance.

First, the sponsor will submit all TEE reports as expedited reports and TEE reports will be analyzed in the periodic reports. Also, the sponsor has developed a questionnaire to gather information on TEE cases and risk factors. Clarification on how this questionnaire would be administered would be useful.

The sponsor has proposed a pregnancy registry to assess the adverse effects (if any) which might be observed following prenatal exposure to HyQvia. This method is reasonable, but CBER/OBE cannot further assess the proposal until a protocol is submitted.

A second questionnaire has been designed to follow-up reports of immunological reactions. Clarification on how this questionnaire would be administered would be useful.

Finally, the sponsor has proposed a study to assess possible long term effects of anti-PH20 antibodies. CBER/OBE cannot assess this proposal until a protocol is submitted. Given the current evidence and the possibility that effects may not be evident for an extended period (years) or only under specific conditions (CNS injury and remyelination), this study may be impractical due to the need for frequent follow-up, the risk of a high number of patients being lost to follow-up over time, and the associated costs. If other issues preventing HyQvia approval were to be resolved, a careful assessment of this study protocol would be necessary to ensure that the study design was appropriate to assess the safety issue.