CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761304Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 20, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761304
Product Name, Dosage Form, and Strength:	Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) injection, 1,008 mg and 11,200 units/5.6 mL (180 mg and 2,000 Units per mL)
Applicant/Sponsor Name:	Argenx BV
TTT ID #:	2022-1755-3
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on June 16, 2023 for Vyvgart Hytrulo. The Division of Neurology 1 (DN 1) requested that we review the revised carton labeling for Vyvgart Hytrulo (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous review.[a]

2 CONCLUSION

The revised carton labeling is acceptable from a medication error perspective. We have no additional recommendations at this time.

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Whaley, E. Labeling Memo for Vyvgart Hytrulo (BLA 761304). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JUN 15. TTT ID No.: 2022-1755-2.

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06/20/2023 09:52:10 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	June 16, 2023
Reviewer:	Silvia Perez-Vilar, PhD, PharmD Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD, MA Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	VYVGART HYTRULO™ (efgartigimod alfa and hyaluronidase-qvfc)
Application Type/Number:	BLA 761304
Applicant/sponsor:	Argenx BV
TTT #:	2023-3327

Expedited ARIA Sufficiency for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

In December 2021, the U.S. Food and Drug Administration approved efgartigimod alfa – fcab (VYVGART™, Argenx BV)—an intravenously administered neonatal Fc receptor (FcRn) blocker—for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.[1] Besides efgartigimod alfa – fcab, currently FDA-approved treatments for myasthenia gravis include pyridostigmine bromide and eculizumab. Other treatments include prednisone, azathioprine, mycophenolate mofetil, tacrolimus, rituximab, plasmapheresis, and intravenous immunoglobulin, and thymectomy. [2]

VYVGART's applicant has now developed a subcutaneously administered formulation of efgartigimod alfa co-formulated with an approved recombinant human hyaluronidase[3] (efgartigimod alfa and hyaluronidase-qvfc, VYVGART HYTRULO™, Argenx BV). The proposed indication is generalized myasthenia gravis in adult subjects. VYVGART HYTRULO™ will be approved for the treatment of adults with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive. [4] The recommended dosing regimen for VYVGART will be 1,008 mg / 11,200 units (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) administered subcutaneously in cycles of once weekly injections for 4 weeks. Efgartigimod alfa and hyaluronidase are expected to be degraded by proteolytic enzymes into small peptides and amino acids. The terminal half-life is 80 to 120 hours (3 to 5 days). [5]

The Biologic License Application (BLA) submission for VYVGART HYTRULO™ included safety data from 168 adults with generalized myasthenia gravis enrolled in the randomized, open-label, parallel-group study ARGX-113-2001 (91 seropositive for AChR-Ab and 20 seronegative) and the supportive open-label extension study ARGX-113-2002. The safety assessment also included additional supportive safety data from subjects who transitioned from an open-label extension from the approved intravenous (IV) form of efgartigimod (ARGX-113-1705) into Study ARGX-113-2002. Adverse reactions associated with VYVGART HYTRULO™ included injection site and hypersensitivity reactions. Risk of infections appeared to be similar to that in the efgartigimod IV group (Study ARGX-113-2001). [6] The proposed label (as of June 16, 2023) includes Warnings and Precautions (section 5) for infections and hypersensitivity reactions and

[1] U.S. Food and Drug Administration. Drug Approval Package: VYVGART. Approval letter. Accessed on May 22, 2023 at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761195Orig1s000Approv.pdf
[2] U.S. Food and Drug Administration. Drug Approval Package: VYVGART. Other reviews. ARIA Sufficiency. Accessed on May 22, 2023 at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761195Orig1s000TOC.cfm
[3] Endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously
[4] U.S. Food and Drug Administration. Division of Neurology 1. Efgartigimod alfa and hyaluronidase-qvfc (VYVGART HYTRULO™, Argenx BV). Draft review dated May 11, 2023
[5] VYVGART HYTRULO. Proposed U.S. labeling dated June 16, 2023
[6] See footnote 4

lists respiratory tract infections, headache, urinary tract infection, and injection site reactions as common adverse reactions (section 6). [7]

1.2. Describe the Safety Concern

The Division of Neurology 1 (DN1) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of VYVGART HYTRULO™ during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease Control and Prevention 2008, Food and Drug Administration 2014). Myasthenia gravis is a serious, life-threatening, chronic autoimmune disease in which antibodies bind to acetylcholine receptors, muscle-specific kinase, or lipoprotein-related peptide 4 in the postsynaptic membrane at the neuromuscular junction (Gilhus 2016, Koneczny and Herbst 2019). Different antibodies can result in different subgroups of myasthenia gravis with variable phenotypes and severity. In most patients, the antibodies bind to acetylcholine receptors (Gilhus 2020). Coexisting conditions are common; approximately 15% of patients have a second autoimmune disease, 10% have a thymoma, and although rare, myocarditis occurs with an increased frequency in patients with myasthenia gravis (Gilhus 2016). Myasthenia gravis is a rare disorder, with an estimated prevalence in the general population of 150–250 individuals per million, and with an annual incidence of 8–10 individuals per million. Myasthenia gravis with onset below 50 years, thymic hyperplasia, and acetylcholine receptor antibodies is more common in females than in males. As both prevalence and incidence increase with increasing age, the prevalence and incidence are somewhat lower among females of reproductive age. The muscle weakness, the circulating autoantibodies, the hyperplastic thymus, and any autoimmune comorbidity may influence both mother and child health during pregnancy and also during breastfeeding (Gilhus 2020). Despite this, most pregnancy complications occur with a similar frequency in women with and without myasthenia gravis. However, preterm rupture of amniotic membranes shows an increased frequency, and especially in those with myasthenia gravis deterioration during the pregnancy (Gilhus 2020). Around 10% of the newborn develop neonatal myasthenia during the first few days after birth, which is transient and usually mild. In rare cases, transplacental transfer of acetylcholine receptor antibodies leads to permanent muscle weakness in the child, and arthrogryposis with joint contractures (Gilhus 2020).

There are no data on pregnancy exposure during clinical trials to inform the risk of maternal, fetal, and infant outcomes associated with the use of efgartigimod w/ rHuPH20 or efgartigimod alfa – fcab.[8, 9] No new reproductive and developmental toxicity studies were conducted for this application as the studies conducted for the approved IV formulation (efgartigimod alfa – fcab) were considered adequate. As described in the VYVGART current labeling, there is no evidence of adverse developmental outcomes following the administration of VYVGART at up to 100 mg/kg/day in rats and rabbits.[10] At the time of VYVGART approval, FDA issued a post-marketing requirement (PMR 4202-1) for a worldwide descriptive study that collects prospective and retrospective data in women exposed to VYVGART during pregnancy and/or

[7] See footnote 5
[8] See footnote 4
[9] U.S. Food and Drug Administration. Drug Approval Package: VYVGART. Other reviews. ARIA Sufficiency. Accessed on May 22, 2023 at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761195Orig1s000TOC.cfm
[10] VYVGART. U.S. labeling Accessed on May 22, 2023 at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761195s000lbl.pdf

lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. [11]

The currently proposed labeling for VYVGART HYTRULO™, as of June 16, 2023, [12] states in "Section 8.1 (Pregnancy):

"Risk Summary

There are no available data on the use of VYVGART HYTRULO or efgartigimod alfa containing products during pregnancy. There was no evidence of adverse developmental outcomes following the intravenous administration of efgartigimod alfa at up to 100 mg/kg/day in rats and rabbits (see Data).

The background rate of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background rate of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Therefore, efgartigimod alfa may be transmitted from the mother to the developing fetus.

As VYVGART HYTRULO is expected to reduce maternal IgG antibody levels, reduction in passive protection to the newborn is anticipated. Risk and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to VYVGART HYTRULO in utero [see Warnings and Precautions (5.1)].

Data

Animal Data

VYVGART HYTRULO for subcutaneous injection contains efgartigimod alfa and hyaluronidase [see Description (11)].

Efgartigimod alfa:
- *Intravenous administration of efgartigimod alfa (0, 30, or 100 mg/kg/day) to pregnant rats and rabbits throughout organogenesis resulted in no adverse effects on embryofetal development in either species. Maternal efgartigimod alfa exposures at the highest no-effect doses were approximately 8 and 62 times, respectively, that in humans at the recommended human dose (RHD) of 1008 mg.*
- *Intravenous administration of efgartigimod alfa (0, 30, or 100 mg/kg/day) to rats throughout gestation and lactation resulted in no adverse effects on pre- or postnatal development. Maternal exposures at the highest no-effect dose were approximately 13 times that in humans at the RHD.*

[11] See footnote 1
[12] See footnote 5

Hyaluronidase:

- *In a study in which hyaluronidase (recombinant human) was administered by subcutaneous injection to pregnant mice throughout organogenesis, increased embryofetal mortality and decreased fetal body weights were observed at the highest doses tested. The no-effect dose for adverse effects on embryofetal development in the mouse was approximately 1800 times the dose of hyaluronidase at the recommended human dose (RHD) of VYVGART HYTRULO (1,008 mg efgartigimod alfa and 11,200 U hyaluronidase), on a U/kg basis.*
- *There were no adverse effects on pre- and postnatal development following subcutaneous administration of hyaluronidase (recombinant human) to mice throughout gestation and lactation at doses up to 5,000 times the dose of hyaluronidase at the RHD of VYVGART HYTRULO, on a U/kg basis."*

The language in Section 8.2 (Lactation) is as follows:

"Risk Summary

There is no information regarding the presence of efgartigimod alfa or hyaluronidase, from administration of VYVGART HYTRULO, in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYVGART HYTRULO and any potential adverse effects on the breastfed infant from VYVGART HYTRULO or from the underlying maternal condition."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of

statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Descriptive pregnancy safety study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: ARIA lacks the capacity to identify lactating women.

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Covariates: ARIA does not have detailed information on potential confounders. The descriptive pregnancy safety study being considered would collect detailed narratives with information on potential covariates, such as IgG anti-acetylcholine receptor antibodies, baseline motor strength, cardiac and respiratory status, and pulmonary function tests, and lifestyle factors, such as prenatal supplement use and iodine intake.

Analytical tools: ARIA analytical tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by DN1, as of May 11, 2023, for the PMR related to pregnancy outcomes:

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to VYVGART HYTRULO (efgartigimod alfa and hyaluronidase-qvfc) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

3. REFERENCES

Centers for Disease Control and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep **57**(1): 1-5.

Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved November 24, 2021, from https://www.fda.gov/media/90160/download.

Gilhus, N. E. (2016). "Myasthenia Gravis." N Engl J Med **375**(26): 2570-2581.

Gilhus, N. E. (2020). "Myasthenia Gravis Can Have Consequences for Pregnancy and the Developing Child." Front Neurol **11**: 554.

Koneczny, I. and R. Herbst (2019). "Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture." Cells **8**(7).

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/s/

SILVIA PEREZ-VILAR
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SILVIA PEREZ-VILAR on behalf of CATHERINE L CALLAHAN
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SUKHMINDER K SANDHU
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JUDITH W ZANDER
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PATRICIA L BRIGHT
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ROBERT BALL
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 2023

TO: Teresa Buracchio, M.D.
Deputy Director
Division of Neurology I (DN I)
Office of Neuroscience (ON)
Office of New Drugs (OND)

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Director/Deputy Director
DGDSI
OSIS

SUBJECT: Remote regulatory assessment (RRA) of (b) (4) (b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of the analytical portions [i.e., Anti-drug antibody (ADA), Neutralizing Antibody (NAb) and total IgG and anti-AchR antibody (PD)] of the study ARGX-113-2001 (BLA 761304) conducted at (b) (4) (b) (4)

I observed the following objectionable conditions during the RRA:

1. (b) (4)
2.

Based on my review of the objectionable conditions and the firm's response to the RRA observations, I conclude that the observation #1 impacts the reliability of data from the twelve hemolyzed subject samples assessed for detection of ADA, NAb, and evaluated for PD. However, since the objectionable condition

#1 was isolated from the assessment of hemolyzed samples during ADA, NAb and PD studies, the condition #1 did not impact the reliability of data from non-hemolyzed subject samples. Therefore, the data from ARGX-113-2001, excluding the twelve hemolyzed subject samples (see **Attachment 6** for applicable subject numbers), are reliable.

I also conclude that the observation #2 has no impact on the reliability of the NAb study sample data.

2. Reviewed Studies

ARGX-113-2001 (BLA 761304)
"A Phase 3, Randomized, Open-label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple Intravenous Infusions of Efgartigimod in Patients with Generalized Myasthenia Gravis"
Sample Analysis Period for:
PD (CP200434): Sep 14, 2021 – Feb 9, 2022
ADA (CP200435): Nov 15, 2021 – Mar 8, 2022
NAb (CP200435): Dec 3, 2021 – Mar 8, 2022

3. Scope of RRA

From [redacted] (b) (4) OSIS scientist Hasan A. Irier reviewed the analytical portion of the above studies conducted at [redacted] (b) (4)
The RRA included an examination of records and processes for method validations, and study sample analysis conducted as part of PD, ADA and NAb studies. The RRA also included a review of SOPs, analytical study plans (ASPs), sample management and receipt, method validations, and study data, and discussions with management, study directors, and [redacted] (b) (4) staff involved in these studies via ZoomGov.

4. RRA Observations

At the conclusion of the RRA, I observed two objectionable conditions. I discussed the following items with the firm's management during the RRA close-out meeting. The firm responded to these observations on [redacted] (b) (4) (**Attachment 1**).

My evaluation of the observations and the firm's response is presented below.

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KIMBERLY A BENSON
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 15, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761304
Product Name, Dosage Form, and Strength:	Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) injection, 1,008 mg and 11,200 units/5.6 mL (180 mg and 2,000 Units per mL)
Applicant/Sponsor Name:	Argenx BV
TTT ID #:	2022-1755-2
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label and carton labeling received on June 12, 2023 for Vyvgart Hytrulo. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Vyvgart Hytrulo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous review.[a]

2 CONCLUSION

The revised container label is acceptable from a medication error perspective. The Applicant provided additional information (b) (4) We considered the Applicant's additional information and continue to recommend that the proposed product is labeled for

[a] Whaley, E. Labeling Memo for Vyvgart Hytrulo (BLA 761304). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAY 31. OSE RCM No.: 2022-1755-1.

HCP administration (b) (4) Therefore, the carton labeling is unacceptable from a medication error perspective, and we provide a recommendation in Section 3 below.

3 RECOMMENDATIONS FOR ARGENX BV

We recommend the following be implemented prior to approval of BLA 761304:

Table 1: Identified Issues and Recommendations for Argenx BV			
	Identified Issue	Rationale for Concern	Recommendation
Carton labeling			
1.	As previous noted, the carton labeling does not indicate that the product is for healthcare professional (HCP) administration only.	An HCP administration only statement will help alert patients, caregivers, and HCPs (particularly pharmacies who may dispense the product directly to the patient) that the patient should take the product to their HCP for administration.	We recommend adding the statement "Must be administered by a healthcare provider" to the principal display panel of the carton labeling.

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APPENDIX B. APPLICANT'S RESPONSE TO LABELING COMMENTS RECEIVED ON JUNE 12, 2023

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 2, 2023

To: Michael Matthews, Regulatory Project Manager, Department of Neurology 1 (DN1)

Rainer Paine, Clinical Reviewer, DN1

Tracy Peters, Associate Director for Labeling, DN1

From: Sapna Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for VYVGART HYTRULO™ (efgartigimod alfa and hyaluronidase-qvfc) injection, for subcutaneous use

BLA: 761304

Background: In response to DN1's consult request dated October 13, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original BLA submission for VYVGART HYTRULO™ (efgartigimod alfa and hyaluronidase-qvfc) injection, for subcutaneous use (Vyvgart Hytrulo).

PI: OPDP's review of the proposed PI is based on the draft labeling emailed to the OPDP by DN1 (Michael Matthews) on May 19, 2023, and our comments are provided below.

Carton and Container Labeling: OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on May 18, 2023, and our comments are provided below

Thank you for your consult. If you have any questions, please contact Sapna Shah at 240-402-6068 or Sapna.Shah@fda.hhs.gov.

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/s/

SAPNA SHAH
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 31, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761304
Product Name, Dosage Form, and Strength:	Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) injection, (b) (4) mg and 11,200 units/5.6 mL (180 mg and 2,000 Units per mL)
Applicant/Sponsor Name:	Argenx BV
TTT ID #:	2022-1755-1
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label and carton labeling received on May 18, 2023 for Vyvgart Hytrulo. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Vyvgart Hytrulo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations sent to the Applicant as part of a May 8, 2023 Information Request (IR).[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. Specifically, the root proprietary name "Vyvgart" and the proprietary name modifier "Hytrulo" are not presented in the same font size and thus do not have equal prominence. We are concerned that this may pose risk of product selection errors between Vyvgart Hytrulo and the approved product Vyvgart. Additionally, we acknowledge the Applicant indicated use of the expiration date format YYYY-MM due to space limitations; however, the

[a] Matthews, M. Information Request for Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc). Silver Spring (MD): FDA, CDER, OND, DN1 (US); 2023 MAY 8. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806c9f49.

Applicant did not clarify whether the expiration format will include a mix of numbers and letters or all numerical characters.

3 RECOMMENDATIONS FOR ARGENX BV

We recommend the following be implemented for this BLA 761304:

Table 1: Identified Issues and Recommendations for Argenx BV			
	Identified Issue	Rationale for Concern	Recommendation
Container Label and Carton labeling			
1.	The root proprietary name "Vyvgart" and the proprietary name modifier "Hytrulo" are not presented in the same font size and thus do not have equal prominence.	Confusion regarding the proprietary name of the product poses risk of product selection errors (i.e., between Vyvgart Hytrulo and Vyvgart).	Revise the font size used for the root proprietary name "Vyvgart" and the proprietary name modifier "Hytrulo" so that they appear with equal prominence.
2.	It is unclear whether the proposed expiration date format (i.e., YYYY-MM) will include a mix of numbers and letters or all numerical characters.	To minimize confusion and reduce the risk for deteriorated drug medication errors, clarify the format you intend to use.	Clarify how your proposed expiration date format (i.e., YYYY-MM) will be presented. Please note the expiration date may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if letter characters are used to represent the month.[b]

[b] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2021. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 18, 2023

TO: Teresa Buracchio, MD
Deputy Director
Division of Neurology I (DN I)
Office of Neuroscience (ON)
Office of New Drugs (OND)

FROM: Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Wielospecjalistyczna Poradnia Lekarska Synapsis, Katowice, Poland.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study ARGX-113-2001 (BLA 761304) conducted at Wielospecjalistyczna Poradnia Lekarska, Katowice, Poland.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out.

After reviewing the inspectional findings, I conclude the data from the audited study is reliable.

2. Inspected Study:

BLA 761304

Study Number: ARGX-113-2001
Study Title: "A Phase 3, Randomized, Open-label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple

Intravenous Infusions of Efgartigimod in Patients with Generalized Myasthenia Gravis"

Dates of conduct (at Katowice site): 5/6/2021 (first subject screened) – 8/31/2021 (last study visit)

Clinical site: Wielospecjalistyczna Poradnia LekarskaSynapsis
Czerwinskiego 8
40-123 Katowice
Slaskie, Poland

3. Inspectional Findings

ORA investigator Brandy D. Brown inspected Wielospecjalistyczna Poradnia Lekarska, Katowice, Poland, from March 27-31, 2023.

This was the first OSIS inspection of Wielospecjalistyczna Poradnia Lekarska under the BA/BE program.

The current inspection included auditing the following items:

-Source record documentation
-Informed consent procedures
-Protocol adherence & deviations
-Independent Ethics Committee (IEC) approvals
-Adverse event reporting and follow up
-Monitoring
-Test article accountability, storage, and dispensing
-Facilities
-Study personnel training
-Subject sample collection & processing
-Randomization

At the conclusion of the inspection, investigator Brandy D. Brown did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

Makini Cobourne-Duval, Ph.D.
Pharmacologist

Draft: MCD 5/15/2023, 5/16/2023, 5/18/2023
Edit: DP 05/16/2023; JC 05/16/2023

OSIS File #: BE 9765

eNSpect Assignment ID: 218131
eNSpect OpID: 246311

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 19, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761304
Product Type: Drug Constituent Name and Strength	Multi-ingredient product Vyvgart Hytrulo[a] (efgartigimod alfa and hyaluronidase-qvfc[b]) injection, (b) (4) mg and 11,200 units/5.6 mL (180 mg and 2,000 Units per mL)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Argenx BV
Submission Date:	9/20/22
TTT ID #:	2022-1755; 2022-1807
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Director:	Danielle Harris, PharmD

[a] The proprietary name "Vyvgart Hytrulo" was found conditionally acceptable for this BLA 761304 on March 16, 2023.
[b] The nonproprietary name "efgartigimod alfa and hyaluronidase-qvfc" was found conditionally acceptable for this BLA 761304 on February 17, 2023.

1 EXECUTIVE SUMMARY

The human factors validation study (HFVS) results report and supplemental HFVS report (collectively referred to as the human factors [HF] validation studies) for Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) (b) (4) we recommend (b) (4) administration to health care providers (HCPs) (b) (4)

We carefully reviewed each use-related event, the Applicant's use-related risk analysis (URRA), the root cause analysis, the participants' subjective feedback, the Applicant's proposed risk mitigations (if applicable), and the Applicant's discussion of residual risk. (b) (4)

(b) (4)

We discussed our findings with the Division of Neurology 1 (DN 1); the DN 1 review team aligns with our concern (b) (4) considered that the critical tasks required in the use of the proposed product align with the scope of practice routinely practiced by HCPs (e.g., withdraw the dose from the vial and administer

subcutaneously using a separately supplied 10 mL syringe, transfer needle, and winged infusion set). (b) (4) we recommend that the proposed product be labeled (b) (4) administration to HCPs only. We find HFVS data is not needed to support the safe and effective use of the proposed product by HCPs in this particular instance because based on the general experience and medical expertise of HCPs, we anticipate HCPs will be familiar with similar approved products with similar preparation and administration tasks. Therefore, we employed our labeling best practices to determine if labeling mitigations are necessary to further ensure the PI, container label, and carton labeling (see Section 4.2 below) are designed to ensure safe and effective use considering the HCP as the intended user.

(b) (4)

2 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports and labels and labeling submitted under BLA 761304 for Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) injection.

2.1 PRODUCT DESCRIPTION

Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) injection is a multi-ingredient product that is intended for treatment of gMG in adult patients.

The proposed product will be supplied as a single-dose vial containing efgartigimod alfa (b) (4) mg and hyaluronidase- 12,000 Units in 5.6 mL. The product is withdrawn from the vial and administered subcutaneously using a separately supplied 10 mL syringe, transfer needle, and winged infusion set. (b) (4)

(b) (4)

[redacted] (b) (4)

2.2 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM[c]

- On July 8, 2021, the Applicant submitted an HFVS protocol under IND 152843. Subsequently, we determined that it was premature to evaluate the submitted HFVS protocol, and we considered the protocol withdrawn.[d]
- On October 14, 2021, the Applicant submitted an HFVS protocol under IND 152843. We completed our review of the HFVS protocol on March 17, 2022[e] and provided recommendations for the Applicant.
- In a July 12, 2022 Type C teleconference, we referred the Applicant to the March 22, 2022 HF Validation Study Protocol – Advice Letter and to the Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications draft guidance. We also informed the Applicant to submit the HF study to eCTD section 5.3.5.4 – Other Study reports and related information.[f]
- On September 20, 2022, as part of the BLA 761304 submission, the Applicant submitted the HFVS results report, which is the subject of this review.
- On November 17, 2022, the Agency communicated a potential HF-related review issue [redacted] (b) (4) in the Filing Review Issues Identified letter.[g]

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

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[c] On July 8, 2022, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the terms, Vyvgart, IND 152843 and BLA 761304. We considered our previous recommendations to see if they are applicable for this current review.

[d] Whaley E. HF Protocol Validation Study Protocol Withdrawal Memo for efgartigimod alfa and hyaluronidase injection IND 152843. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUL 26. RCM No.: 2021-1379.

[e] Whaley E. HF Protocol Validation Study Protocol Review for efgartigimod alfa and hyaluronidase injection IND 152843. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 MAR 17. RCM No.: 2021-2018.

[f] Matthews, M. Type C Meeting Minutes for efgartigimod (ARGX-113) with recombinant human hyaluronidase PH20 (rHuPH20). Silver Spring (MD): FDA, CDER, ORO, DRON, DN1 (US); 2022 AUG 8. IND 152843. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8067ad38

[g] Matthews, M. Filing Review Issues Identified for ARGX-113 with recombinant human hyaluronidase PH20 (rHuPH20) BLA 761304. Silver Spring (MD): FDA, CDER, ON, DN1 (US); 2022 NOV 17. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80699a3e

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information on Human Factors Engineering (HFE) Process	B
Human Factors Validation Study Report	C
Information Requests	D
Labels and Labeling	E

4 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the user interface supports the safe and effective use of the proposed product.

(b) (4)

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