CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761195Orig1s000

OTHER REVIEW(S)

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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:	December 15, 2021
Reviewer:	Silvia Perez-Vilar, PharmD, PhD Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Deputy Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	VYVGART™ (efgartigimod alfa – fcab)
Application Type/Number:	BLA 761195
Applicant/sponsor:	Argenx BV
OSE RCM #:	2021-2292

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

1. BACKGROUND INFORMATION

1.1. Medical Product

Efgartigimod alfa – fcab (VYVGART™, Argenx BV) is an intravenously administered human IgG1 antibody fragment that binds to the neonatal Fc receptor (FcRn) resulting in the reduction of circulating immunoglobulin G (IgG) including IgG autoantibodies. Efgartigimod does not reduce the levels of other immunoglobulins (IgA, IgD, IgE, or IgM), or those of albumin. Each 20 mL single-dose vial contains 400 mg of efgartigimod alfa – fcab at a concentration of 20 mg/mL. It is a new molecular entity (NME) not currently approved or marketed in any country. The proposed indication is for the treatment of adult patients with generalized myasthenia gravis. VYVGART will be approved for the treatment of adults with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive. Currently FDA-approved treatments for myasthenia gravis include pyridostigmine bromide and eculizumab. [1] Treatments such as prednisone, azathioprine, mycophenolate mofetil, tacrolimus, rituximab, plasmapheresis, and intravenous immunoglobulin are used off-label. Thymectomy is also a treatment option for some patients. [2]

The proposed dosing regimen for VYVGART is 10 mg/kg as a 1-hour intravenous infusion to be administered in treatment cycles of once weekly infusions for 4 weeks. Efgartigimod alfa – fcab exhibits linear pharmacokinetics and is 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). [3]

The Biologic License Application (BLA) submission included safety data on adults with generalized myasthenia gravis exposed to at least one dose of efgartigimod alfa – fcab during enrollment in an exploratory phase 2, double-blind, placebo-controlled, randomized clinical trial, a pivotal phase 3, double-blind, placebo-controlled, randomized clinical trial, and/or a Phase 3 long-term open label, single-arm multicenter study. Common adverse reactions associated with treatment included respiratory tract infections, urinary tract infections, myalgia, headaches, and hypo/hyperesthesia. [4] The proposed label (as of December 15, 2021) includes warnings and precautions for infections and hypersensitivity reactions. [5]

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 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

[1] Eculizumab is indicated for treatment of acetylcholine receptor myasthenia gravis, but is not indicated for muscle specific kinase antibody positive or low-density lipoprotein receptor-related protein 4 antibody positive patients.
[2] Efgartigimod alfa – fcab (VYVGART™, Argenx BV). Draft integrated review dated November 23, 2021. Division of Neurology 1. U.S. Food and Drug Administration
[3] Proposed VYVGART labeling dated December 15, 2021
[4] See footnote 2
[5] See footnote 3

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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. 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. 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 alfa – fcab.[6] A full battery of reproductive toxicology studies was conducted in Sprague-Dawley rats and New Zealand White rabbits. In all studies, efgartigimod alfa – fcab was administered by intravenous injection at doses of 0, 30, or 100 mg/kg. Efgartigimod alfa – fcab was administered daily to male rats (20/group) beginning 4 weeks prior to mating until the day before sacrifice on study day 43 or 44 and to females (20/group) beginning 2 weeks prior to mating until gestational day 7; there were no effects on the number of females pregnant, females with live fetuses, or the number of resorptions. When pregnant rats (25/group) were administered efgartigimod alfa – fcab daily from gestational day 6 to gestational day 17, no effects on embryofetal development were observed. A slight dose-related increase in pre-implantation loss was noted. Pregnant rabbits (20/group) received efgartigimod alfa – fcab daily from gestational day 6 to gestational day 28. Two low dose females (gestational day 28; 9.1% incidence) and one high dose female (gestational day 20; 4.8% incidence) aborted. This rate was slightly greater than the historical spontaneous abortion rate at this facility (4.26% ± 4.18 with a range of 0.0 to 9.5%). There were no significant effects on Cesarean parameters or on embryofetal development. Cerebral hemorrhage was observed in three high dose pups in different litters (15% litter incidence). The total fetal incidence was within the historical control range; however, litter incidence for historical controls was not provided. Another animal study administered efgartigimod alfa – fcab daily to pregnant rats (25/group) from gestational day 6 to lactation day. One pregnant rat who received the high dose died prematurely (gestational day 21). This death was considered due to "incipient abortion." No test article-related effects were observed on gestation length, gestation index, or preweaning litter parameters (including implantation, liveborn pups,

[6] See footnote 2

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

postnatal survival). There were also no drug-related effects on postnatal developmental landmarks or neurobehavioral function. However, the learning and memory evaluation did not include a complex maze as is usually expected. There were no significant effects on mating parameters in offspring or on F2 fetal development. There was a slight reduction in the number of pregnant F1 females, but the effect was not dose-related in magnitude. [7]

The currently proposed labeling, as of December 15, 2021, [8] states in "Section 8.1 (Pregnancy):

"Risk Summary

There are no available data on the use of VYVGART during pregnancy. There is no evidence of adverse developmental outcomes following the administration of VYVGART 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 semester. Therefore, efgartigimod alfa-fcab may be transmitted from the mother to the developing fetus.

As VYVGART 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 in utero [see Warnings and Precautions (5.1)].

Data
Animal Data

Intravenous administration of efgartigimod alfa-fcab (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. The doses tested are 3 and 10 times the recommended human dose (RHD) of 10 mg/kg, on a body weight (mg/kg) basis.

Intravenous administration of efgartigimod alfa-fcab (0, 30, or 100 mg/kg/day) to rats throughout gestation and lactation resulted in no adverse effects on pre- or postnatal development. The doses tested are 3 and 10 times the recommended human dose (RHD) of 10 mg/kg, on a body weight (mg/kg) basis."

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

[7] Efgartigimod alfa – fcab (VYVGART™, Argenx BV). Non-clinical appendix to draft integrated review dated November 23, 2021. Division of Neurology 1. U.S. Food and Drug Administration
[8] See footnote 3

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.