Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

ADDENDUM MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Epidemiology (OBE) Center for Biologics Evaluation and Research (CBER)
From:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Grifols
Product:	GAMUNEX-C (Immune Globulin Injection (Human), 10%, Caprylate/Chromatography Purified)
STN:	125046/1709
Indication:	For use in Primary Humoral Immunodeficiency (PI), Idiopathic Thrombocytopenic Purpura (ITP) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
Meeting Date:	Pediatric Advisory Committee Meeting, September 2020

Contents

1 INTRODUCTION

Please see Gamunex-C Safety and Utilization Review memorandum (dated February 2020), for a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review is the December 4, 2015 approval of the GAMUNEX-C efficacy supplement (STN 125046/1325) to expand the indication to include subcutaneous administration in pediatric patients (ages 2 to 16 years) with primary humoral immunodeficiency. The Gamunex-C postmarketing pediatric safety data was initially scheduled to be presented at the April 2020 Pediatric Advisory Committee (PAC) meeting which was later postponed to September 2020 due to the Coronavirus Disease 2019 (COVID-19) public health emergency (PHE) declared by the Secretary of Health and Human Services (HHS) on January 31, 2020[1].

The primary PAC memorandum documented the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature during the PAC review period from December 4, 2015 to August 31, 2019. This addendum memorandum documents review of AE reports in passive surveillance data during an additional period since the prior PAC review, from September 1, 2019 to June 1, 2020.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for GAMUNEX-C during September 1, 2019 to June 1, 2020

3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for GAMUNEX-C during the review period, September 1, 2019 to June 1, 2020.

4 ADVERSE EVENT REVIEW

4.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of GAMUNEX-C between September 1, 2019 to June 1, 2020. FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers.

[1] https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx

Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

4.2 Results

The results of the FAERS search of AE reports for GAMUNEX-C during the review period September 1, 2019 to June 1, 2020 are listed in Table 1 below. There were 304 reports, including 303 US reports and 1 foreign report. There were 23 pediatric reports.

Table 1: FAERS Reports for GAMUNEX-C during September 1, 2019 to June 1, 2020

Age	Serious non-fatal, U.S.	Serious Non-fatal, Foreign	Deaths, U.S.	Deaths, Foreign	Non-Serious, U.S.	Non-Serious Foreign	Total, U.S.	Total, Foreign
≤ 16 years	11	1	0	0	11	0	22	1
> 16 years	60	0	12	0	155	0	227	0
Unknown	15	0	2	0	37	0	54	0
All ages	86	1	14	0	203	0	303	1

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, significant disability or otherwise medically important conditions.

4.2.1 Deaths

There were 14 deaths following GAMUNEX-C during the review period; none involved pediatric patients. Fatal reports were individually reviewed and are summarized below.

- 80-year-old woman hospitalized 3 weeks after last Gamunex-C infusion due to “increased labored breathing and high heart rate” was reported to have died.
- 66-year-old woman who had been receiving Gamunex-C since 2016, reported to have “passed away suddenly and unexpectedly” in 2019.
- 66-year-old man who had been receiving Gamunex-C since 2017 was reported to have died a month after last Gamunex-C infusion.
- 55-year-old man who had been receiving Gamunex-C since 2018 was reported to have died in 2019.
- 54-year-old man who had received Gamunex-C for treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) was reported to have died.
- 59-year-old woman who had received Gamunex-C for treatment of common variable immune deficiency was reported to have died.
- 91-year-old man hospitalized for pneumonia was reported to have died.
- 69-year-old woman hospitalized for urinary tract infection was reported to have died.

- 79-year-old man who had received Gamunex-C for 1.5 years was reported to have experienced pain with swelling of hands and fingers and was “bedridden” the day after an infusion of Gamunex-C on an unknown date. Patient was reported to have later died.
- 64-year-old woman who had received Gamunex-C for treatment of an immunodeficiency was reported to have died.
- 75-year-old woman who had received Gamunex-C for treatment of myasthenia gravis was reported to have died.
- 39-year-old man was reported to have died.
- Patient of unknown age who had received Gamunex-C for treatment of common variable immunodeficiency was reported to have died.
- Patient of unknown age reported to have died.

Reviewer comment: Reports contain minimal case details and lack information on the cause of death, and several patients had underlying conditions that may have contributed to fatal outcomes. Deaths were not attributed to Gamunex-C.

4.2.2 Serious Non-fatal Reports

During the review period, there were 87 serious, non-fatal reports; 12 of which involved pediatric patients. The top Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) reported in > 2 pediatric serious non-fatal reports included *Urticaria* (N = 4) and *Infusion related reaction* (N = 3). The top PTs reported in > 9 adult serious non-fatal reports included *Urticaria* (N = 15); *Pruritus* (N = 12); *Rash* (N = 10) and *Headache* (N = 10).

Most reported PTs for both pediatric and adult non-fatal serious AEs are labeled events or consistent with an already labeled event. *Urticaria*, *Rash* and *Headache* are labeled under *Adverse Reactions* section. The unlabeled PT for *Infusion related reaction* is a non-specific term, but could represent a hypersensitivity reaction (*Hypersensitivity* is labeled under Warnings and Precautions and Postmarketing Experience sections). The unlabeled PT for *Pruritus* is consistent with labeled event *Itching* under Adverse Reactions section.

4.2.3 Increased hypersensitivity reactions associated with certain product lots

Eight lots were withdrawn prior to January 2020; these 8 lots and the corresponding adverse event reports are discussed fully in the primary PAC review memorandum. Since January 1, 2020 to June 1, 2020, there have been no additional voluntary lot withdrawals. FDA continues to closely monitor all reports of hypersensitivity, including lot-specific analyses, and has required Grifols to submit expedited 15-day reports for all hypersensitivity events (regardless of seriousness). Since January 1, 2020, most lots have had the expected (i.e., baseline) number of reports of hypersensitivity reactions, and none have had more than 2 – 3 serious reports.

The manufacturer continues to closely monitor reports of hypersensitivity with all product lots to identify any further occurrences. The manufacturer is working with the

FDA to evaluate manufacturing processes, donor materials, and other factors that may be contributing to the observed hypersensitivity reactions.

4.2.4 Non-serious Reports

During September 1, 2019 to June 1, 2020, there were 203 non-serious reports. Eleven reports involved pediatric patients and the most frequent PTs reported in >2 pediatric reports include *Urticaria* (N = 7); *Pruritus* (N = 3) and *Rash* (N = 3). These events appeared among the most frequently reported PTs for serious non-fatal reports and were previously discussed (please see section 4.2.2).

5 CONCLUSION

The PAC review was initiated due to the December 4, 2015 approval of GAMUNEX-C via subcutaneous administration in pediatric patients (ages 2 to 16 years) with primary humoral immunodeficiency.

This addendum memorandum documents review of AE reports in passive surveillance data from September 1, 2019 to June 1, 2020, an additional period since the prior PAC review. There have been no additional voluntary lot withdrawals beyond those discussed in the prior PAC review. There were no substantive differences between the prior PAC review period (December 4, 2015 to August 31, 2019) and this additional review period (September 1, 2019 to June 1, 2020) with respect to the types and frequencies of adverse events. FDA is engaged in ongoing discussions with the manufacturer regarding root cause analysis and investigation of implicated lots. Hypersensitivity reaction is adequately described in the Gamunex-C package insert. FDA will continue to review spontaneous reports of hypersensitivity-type events and conduct lot-specific analysis of adverse event reports as part of continued routine safety monitoring.

6 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of GAMUNEX-C.