

Pediatric Advisory Committee (PAC) Meeting September, 2020

GAMUNEX-C: Hypersensitivity reactions in patients receiving certain product lots

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Outline



- Background
- Adverse Events (AEs) during PAC review period
- Hypersensitivity reactions in patients receiving certain product lots
- Conclusions & FDA Recommendations
- Question for the PAC

Background



- Product: Gamunex-C [Immune Globulin (Human), 10%
 Caprylate/Chromatography Purified]
- Sponsor: Grifols Therapeutics, LLC
- Initial FDA approval: August 27, 2003
- Indications: For use on Primary Humoral Immunodeficiency (PI),
 Idiopathic Thrombocytopenic Purpura (ITP), & Chronic
 Inflammatory Demyelinating Polyneuropathy (CIDP)
- Trigger for PAC review: December 4, 2015 Approval of expanded indication to include subcutaneous route of administration in pediatric patients (ages 2 to 16 years) with PI

Adverse Events (AEs) during PAC review period PAC (December 4, 2015 – August 31, 2019)



| Age | Serious | Serious | Deaths, | Deaths, | Non- | Non- | Total, | Total, |
|----------|------------|---------|---------|---------|----------|---------|--------|---------|
| | non-fatal, | Non- | U.S. | Foreign | Serious, | Serious | U.S. | Foreign |
| | U.S. | fatal, | | | U.S. | Foreign | | |
| | | Foreign | | | | | | |
| ≤ 16 | 38 | 3 | 2 | 0 | 52 | 0 | 92 | 3 |
| years | | | | | | | | |
| > 16 | 296 | 21 | 10 | 5 | 654 | 0 | 960 | 26 |
| years | | | | | | | | |
| Unknown | 42 | 16 | 3 | 0 | 247 | 0 | 292 | 16 |
| | | | | | | | | |
| All ages | 376 | 40 | 15 | 5 | 953 | 0 | 1344 | 45 |
| | | | | | | | | |



Addendum: updated review of AEs (September 1, 2019 – June 1, 2020)

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

Pediatric AEs during PAC review period (December 4, 2015 – August 31, 2019)



| Total | 95 |
|-----------------|------|
| Deaths | 2* |
| Non-fatal SAEs | 41** |
| Non-serious AEs | 52 |

- FDA reviewed individual narratives of all deaths, serious pediatric reports, and most frequently reported Preferred Terms (PTs)
- Most common AEs occurring with a frequency ≥5 reports, for non-fatal SAEs included: Urticaria, Infusion related reaction, Dyspnea, Rash, Hemolytic anemia, Headache, Hypotension, Pyrexia

^{*} Deaths occurred in U.S., are not related to withdrawn lots, & patients had other comorbidities that suggest etiologies other than Gamunex-C for deaths

^{**} This number includes 11 serious adverse events (SAEs) for hypersensitivity reactions associated with voluntary lot withdrawals



Hypersensitivity reactions in certain lots

- From December 4, 2015 through July 2018, less than 2-3 hypersensitivity-type AE reports per lot
- No withdrawals or recalls up to August 2018
- August 2018: increase in hypersensitivity-type AE reports associated with specific lots
- Most common AEs- urticaria, pruritus, rash & lip swelling
- Onset during infusion or shortly thereafter
- Some resolve spontaneously, others require treatment on-site or in ED with antihistamines and/or steroids*

^{*} Of note, there are varying pre-treatment protocols at different infusion centers so some patients had been pre-treated and others had not.



Hypersensitivity is a known risk and a labeled event

| Lot # | Total Reports | Pediatric Reports | Voluntary | |
|------------|-----------------------|----------------------|-----------------|--|
| | | | Withdrawal Date | |
| A1GLB01272 | 17, including 10 SAEs | 1 SAE | 16-Aug-2018 | |
| A4GLC01062 | 78, including 46 SAEs | 10, including 9 SAEs | 5-Dec-2018 | |
| A1GLC01372 | 14, including 3 SAEs | 0 | 21-Feb-2019 | |
| A4GLD00502 | 41, including 13 SAEs | 2, including 1 SAE | 28-Jun-2019 | |
| B1GLC01592 | 40, including 23 SAEs | 0 | 21-Aug-2019 | |
| A1GLD00622 | 28, including 3 SAEs | 1 (non-serious AE) | 5-Nov-2019 | |
| A4GKD00232 | 22, including 5 SAEs | 7, including 4 SAEs | 13-Dec-2019 | |
| B3GKD00483 | 31, including 4 SAEs | 4, including 1 SAE | 30-Dec-2019 | |



Summary of hypersensitivity AEs associated with lot withdrawals

- To date: Total 271 reports of hypersensitivity AEs (adults & children), including 107 serious AEs (SAEs)
- No deaths associated with withdrawn lots
- Total of 25 pediatric hypersensitivity reports:

| SAEs | 16 |
|-----------------|---|
| | [3 cases of anaphylaxis, 2 cases of respiratory |
| | distress (other symptoms not reported), and 11 |
| | cases of urticaria/rash] |
| Non-serious AEs | 9 |

Actions: Certain Product Lots associated with Hypersensitivity Reactions



- Voluntary lot withdrawals initiated by Grifols
- FDA communicated this potential signal of a serious risk with a public posting in September 2019*
- FDA continues to review all hypersensitivity reports and conduct close monitoring by lot
- FDA has enhanced pharmacovigilance activities with expedited reporting of all hypersensitivity reactions
- FDA is engaged in ongoing discussions with Grifols to further evaluate root cause and the investigation of implicated lots

^{*}Link: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/april-june-2019-potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event

Conclusions



- No deaths associated with withdrawn lots of Gamunex-C
- This postmarketing pediatric safety review includes passive surveillance AE reports, the sponsor's periodic safety reports, and the published literature for GAMUNEX-C
- Most AE reports were labeled events and commonly associated with the immune globulin product class
- Hypersensitivity is a known risk and a labeled event
- Since August 2018, there have been 8 voluntary withdrawals for Gamunex-C lots associated with increased hypersensitivity reactions*
- No additional voluntary lot withdrawals since January 1, 2020



FDA Recommendations for Gamunex-C

- Routine safety monitoring
- Close monitoring of all reports of hypersensitivity, including lot-specific analyses
- Continue discussion with manufacturer to further investigate root cause



Question to the PAC

 Does the Committee agree with FDA's conclusions and recommendations?