Pediatric Advisory Committee (PAC) Meeting
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GAMUNEX-C: Hypersensitivity reactions in patients receiving certain product lots

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Outline

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- 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 (December 4, 2015 – August 31, 2019)

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	38	3	2	0	52	0	92	3
> 16 years	296	21	10	5	654	0	960	26
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 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

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* Deaths occurred in U.S., are not related to withdrawn lots, & patients had other comorbidities that suggest etiologies other than Gamunex-C for deaths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 Reactions in Patients Receiving Certain Product Lots*

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

*Links:
https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-recalls-shortages/drugwithdrawal_gamunexc_2018-0822.pdf
https://www.asdhealthcare.com/AsdHealthcare/media/AsdLibrary/pdfs/Grifols-Gamunex-C-10-Recall-Customer-Web-Notice-FINAL-12-7-18.pdf
https://www.gamunex-c.com/en/hcp/search?q=lot%20withdrawal

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

*As of June 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?