Medication Errors and Risk Mitigation Strategies for COVID-19 Emergency Use Authorization Drug Products

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Abstract (revised)

Background: The FDA issued several Emergency Use Authorizations (EUA) for different drug products (DP) to treat or prevent COVID-19. As a condition to the EUA, the FDA required the prescriber or their designee to report to FDA all serious adverse events and medication errors (MEs) potentially related to the use of the authorized DP. However, little is known about the overall ME reporting patterns and mitigation strategies for the EUA DPs.

Purpose: Describe EUA ME reporting trends (types of MEs, contributing factors, report source, outcomes) and regulatory strategies used to mitigate MEs to inform ongoing and future pharmacovigilance activities related to EUA DPs.

Methods: We searched the FDA Adverse Event Reporting System (FAERS) for US ME reports submitted between Mar 27, 2020 and Dec 31, 2022 for the EUA DPs authorized for the treatment or prevention of COVID-19 and listed on the FDA EUA webpage[1]. The reports were categorized by report source, DP name and characteristics (e.g., dosage form, strength, and packaging), type of ME, contributing factors, and outcome. We determined the ME mitigation strategies by reviewing each EUA DP administrative record. Descriptive analyses were performed to identify the ME trends.

Results: FAERS contained 3,747 US ME reports associated with 14 EUA DPs. Nirmatrelvir and ritonavir (Paxlovid), casirivimab/imdevimab (Regen-Cov) and remdesivir (Veklury) were associated with the majority of the reported MEs. The most frequently reported MEs across all EUA DPs were incorrect dose, storage error, incorrect duration of administration, potential drug-drug interaction, wrong technique in product usage, dispensing error, and prescribing error. Contributing factors included both system (e.g., staffing shortages and supply issues) and product specific (e.g., multiple presentations for the same DP) areas. Healthcare providers reported 1,731 of the reports, of which 64% were reported to FDA by EUA sponsors. Approximately 10% of the reports included a serious outcome, however, these outcomes were more likely related to drug therapy or underlying medical conditions (including COVID-19) than a ME. The most commonly used ME mitigation strategies were updates to Fact Sheets (FS), Dear Healthcare Provider (DHCP) letters, and container label/carton labeling revisions.

Conclusion: EUA DPs used in the treatment or prevention of COVID-19 were associated with multiple types of MEs and complex contributing factors unique to the COVID-19 pandemic. ME reporting, surveillance, and coordination with sponsors were important in issuing DHCP letters, updating FS, and revising container labels or carton labeling to minimize and prevent MEs.

Introduction

- On February 4, 2020, the Department of Health and Human Services (HHS) declared a public health emergency related to COVID-19.[2] On March 27, 2020, HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3) and authority was given to FDA to issue EUAs for drugs and biological products.[2]
- As a condition to the EUA that FDA issued for DPs used in the treatment or prevention of COVID-19, FDA required the prescriber or their designee to report to FDA all serious adverse events and MEs potentially related to the use of the authorized DP within 7 days from the healthcare provider's awareness of the event.
- DMAMES evaluated the ME reports in real time to recommend mitigation strategies when warranted to promote safe use of the EUA DPs.
- DMAMES has a robust ME pharmacovigilance program for approved DPs (NDAs, BLAs, ANDAs). However, little is known about the overall ME reporting patterns and mitigation strategies for EUA DPs.
- This project describes ME reporting trends (including types of MEs, contributing factors, report source, outcomes) and regulatory strategies used to mitigate MEs associated with DPs that were authorized for use in the treatment or prevention of COVID-19. The results will inform ongoing and future activities to identify and mitigate MEs related to EUA DPs.

Methods

FAERS Data Collection:

- On January 31, 2023, we searched FAERS for US ME reports submitted between Mar 27, 2020 (date HHS determined that circumstances exist justifying the emergency use of drugs and biological products[2]) to Dec 31, 2022, for DPs authorized for use in the treatment or prevention of COVID-19 and listed on the FDA EUA webpage[1]. The ME reports were identified using the Medical Dictionary for Regulatory Activities (MedDRA), V 25.1 Standardized MedDRA Query (SMQ) *Medication errors (narrow)*.
- We downloaded the reports to Excel, individually reviewed each report, and categorized the type of ME using MedDRA Preferred Terms.
- We excluded reports involving EUA DPs that did not have any ME reports (e.g., Regiocit) or were used for indications other than COVID-19 (e.g., Actemra for rheumatoid arthritis). We also excluded reports involving an event date after an EUA DP received FDA approval for use in the treatment or prevention of COVID-19 (e.g., Veklury), or the report had insufficient information for assessment.
- Descriptive information was collected for each report, including report source, DP name and characteristics (e.g., dosage form, strength, and packaging), type of ME, contributing factors, and outcome.

ME mitigation strategies determination:

- We determined the ME mitigation strategies that were used by FDA by reviewing each DP administrative record. We excluded DPs (baricitinib, tocilizumab, molnupiravir, and Propofol-Lipuro 1%) for which we were unable to identify specific ME mitigation strategies.

Table 1 summarizes the ME reporting trends and identified mitigation strategies.

Table 1: EUA DPs with Identified ME Mitigation Strategies, n = 7

EUA DP[a] (Initial EUA Date)	Report Count	ROA	Dosage Form / Strength	ME Type	ME Mitigation Strategies Used
Remdesivir (Veklury)[b] (May 01, 2020)	251	IV	• Injection, 100 mg/20 mL[c] • For injection, 100 mg lyophilized powder for reconstitution	1. Preparation error 2. Incorrect dose 3. Storage error	• Issued DHCP letters and updated FS to clarify authorized population, dosing, administration, and storage conditions • Revised container label and carton labeling
Casirivimab/ Imdevimab (Regen-Cov) (Nov 21, 2020)	552	IV or SC	• Injection, 600 mg casirivimab and 600 mg of imdevimab per 10 mL (co-formulated) • Injection, 300 mg/2.5 mL, 1,332 mg/11.1 mL (casirivimab) • Injection, 300 mg/2.5 mL, 1,332 mg/11.1 mL (imdevimab)	1. Incorrect dose 2. Single component administered 3. Wrong product administered	• Issued DHCP letters and updated FS to clarify packaging configurations, dosing, administration, and handling • Revised container labels, carton labeling, packaging configurations (dose pack), and formulation (new co-formulation)
Bamlanivimab (Nov 9, 2020); Bamlanivimab and Etesevimab (Feb 09, 2021)	180	IV	• Injection, 700 mg/20 mL (bamlanivimab) • Injection, 700 mg/20 mL (etesevimab)	1. Incorrect dose 2. Preparation error 3. Dispensing error	• Updated FS to clarify dosing, preparation or storage and handling
Sotrovimab (May 26, 2021)	177	IV	• Injection, 500 mg/8 mL	1. Storage error 2. Incorrect dose 3. Wrong product administered	• Verified labeling for storage clarity • Updated FS for recommended dosage
Cilgavimab; Tixagevimab (Evusheld) (Dec 08, 2021)	122	IM	• Injection, 150 mg/1.5 mL (cilgavimab) • Injection, 150 mg/1.5 mL (tixagevimab)	1. Incorrect dose 2. Wrong technique in product usage 3. Administration error	• Issued DHCP letters and updated FS to clarify dosing and administration
Nirmatrelvir; Ritonavir (Paxlovid) (Dec 22, 2021)	1,991	Oral	• Nirmatrelvir tablets, 150 mg • Ritonavir tablets, 100 mg	1. Incorrect dose 2. Incorrect product administration duration /wrong schedule 3. Potential DDI[d]	• Issued DHCP letter and updated FS to clarify dosing, administration, and DDIs • Authorization of additional packaging configuration to support renal dosing • Revised container label and carton labeling to clarify dosing and administration
Bebtelovimab (Feb 11, 2022)	28	IV	• Injection, 175 mg/2 mL	1. Incorrect route of administration 2. Wrong technique in product usage 3. Expired product administered	• Updated FS to clarify dosing, administration, and preparation

DHCP: Dear Healthcare Provider, DDI: Drug-Drug Interaction, ROA: Route of Administration, IV: Intravenous, IM: Intramuscular, SC: Subcutaneous, FS: Fact Sheet

[a] We did not identify ME mitigation strategies for Baricitinib (Olumiant), tocilizumab (Actemra), molnupiravir (Lagevrio), and Propofol-lipuro 1% before March 1, 2023.

[b] Remdesivir was not included on the FDA EUA Webpage[1] but was included in our analysis because it was an EUA DP for management of COVID-19 prior to being approved.

[c] Both remdesivir injection and remdesivir for injection formulations were authorized for emergency use in the management of COVID-19; both formulations are now FDA approved.

[d] Reports coded under MedDRA PTs Contraindicated product administered and Labelled drug-drug interaction (DDI) PTs primarily described potential DDI scenarios and were combined under the term Potential DDI.

Results and Discussion

- FAERS contained 3,742 US ME reports of which 438 were excluded leaving 3,304 reports associated with 11 EUA DPs.
- EUA sponsors submitted most (2,643/3,304) of the ME reports to FDA.
- Healthcare providers reported nearly half (1,731/3,304) of the ME reports, of which most involved EUA injectable DPs. Consumers submitted 1,560/3,304 reports, of which nearly all (1,379/1,560) were associated with Nirmatrelvir tablets;Ritonavir tablets (Paxlovid).
- Approximately 10% of the reports included a serious outcome, however, based on individual case review these outcomes were more likely related to drug therapy or underlying medical conditions (including COVID-19) than a ME.
- Nirmatrelvir tablets;Ritonavir tablets (Paxlovid), casirivimab/imdevimab injection (Regen-Cov), and remdesivir injection (Veklury) were associated with the majority of the reported MEs.

Most Commonly Reported ME Types

- MEs commonly reported across all EUA DPs include incorrect dose (e.g., wrong strength for intended population), incorrect duration, potential drug-drug interactions, storage error (e.g., left at room temperature instead of refrigerated), and dispensing error (e.g., wrong strength or formulation dispensed).
- For EUA injectable DPs, incorrect dose, storage error, preparation error, wrong product, and dispensing error were most commonly reported.
- For EUA oral DPs, incorrect dose, incorrect duration, potential drug-drug interaction, prescribing error, and wrong technique in product usage were most commonly reported.

Contributing Factors

- General contributing factors include lack of barcodes for product verification, electronic health system limitations, fast-paced healthcare provider work environment and staffing shortages, supply issues, bedside drug preparation, frequent updates to FS, and delayed changes to carton labeling and container labels.
- Product specific contributing factors include use of investigational drug container labels (especially early in the public health emergency), confusing packing configurations, multiple packaging presentations for the same product, unclear directions for use, special population considerations, and frequent updates to dosing regimens and stability information.

ME Risk Mitigation Strategies

- Issuance of DHCP letters, updates to Fact Sheets (e.g., DOSAGE AND ADMINISTRATION and HOW SUPPLIED sections), and revisions to the container label and carton labeling were the most common strategies used to mitigate the reported MEs with EUA DPs.
- DPs previously approved by FDA (e.g., baricitinib and tocilizumab) that received EUA for the unapproved uses in the treatment or prevention of COVID-19 had fewer reported errors and no ME mitigation strategies compared to other EUA DPs.

Discussion Point

- EUA DP characteristics (e.g., dosage form, route of administration, packaging), time on the market, setting of use (inpatient vs outpatient), extent of surveillance, medical facility culture, prior approval status, and other factors impact ME reporting and need for mitigation strategies.

Conclusion

This project identified multiple ME types and complex contributing factors associated with EUA DPs used in the treatment or prevention of COVID-19 ME reporting, surveillance, and partnerships with sponsors were important in issuing DHCP letters, updating FS, and revising container labels or carton labeling to minimize and prevent MEs. Future research is needed to determine the effectiveness of strategies to mitigate MEs associated with EUA DPs.

References

1. FDA. Emergency Use Authorizations for Drugs and Non-Vaccine Biological Products. Available at: https://www.fda.gov/drugs/emergency-preparedness-drugs/emergency-use-authorizations-drugs-and-non-vaccine-biological-products. Accessed March 01, 2023.
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