The unmet need for rapid epileptic seizure termination (REST)
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ABSTRACT
Approximately 40% of epilepsy patients will continue to experience breakthrough seizures despite stable antiepileptic drug regimens. Rescue treatments have demonstrated efficacy and safety for select seizure emergencies. Outpatient administered intranasal and rectally delivered medications are regulatory approved for acute repetitive seizures (ARS), and injectable benzodiazepines are indicated for parenteral treatment of established status epilepticus. Despite these advances, no studies have been shown to abort an ongoing seizure following patient or caregiver home administration of therapy at the first clinical sign of seizure onset. Such treatment would require rapid systemic absorption without intravenous access, and evidence of seizure cessation within minutes of administration that is superior to placebo (e.g., seizure self-regulation). Rapid epileptic seizure termination (REST) treatment may apply to multiple seizure emergencies beyond ARS, including focal or generalized seizures preceded by an aura, flurries of absence or myoclonic seizures, or prolonged focal and generalized seizures at high risk of progression to status epilepticus. Novel investigational drug delivery systems have demonstrated feasibility of intraictal delivery and seizure cessation by two minutes. Ongoing randomized trials of REST treatment for diverse seizure emergencies hold the potential to decrease bouts of mental and physical incapacitation in patients with drug-resistant epilepsy.

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1. Introduction

Epilepsy is one of the most common diseases of the central nervous system and uncontrolled epileptic seizures have a negative impact on patient quality of life, increasing risk of injury, death and socioeconomic disadvantage [1–3]. Many patients (60–70%) achieve long-term seizure freedom with titration of a daily multi-therapy antiseizure medication (ASM) regimen. However, it is estimated that up to 40% of newly diagnosed epilepsy patients will continue to experience resistant breakthrough seizures despite stable ASM therapy [4].

There are various phenotypes of seizure emergencies, each of which may present an increased risk for injury, seizure recurrence, progression to status epilepticus, and/or mortality [5–7]. Rescue treatments for two specific seizure emergencies, acute repetitive seizures (ARS) and established status epilepticus, have been systematically studied and are available for clinical use. The ARS therapies may be administered postictally in the outpatient setting upon recognition of cluster seizures and have been shown to prevent or delay subsequent recurrent seizures [8–10]. Status epilepticus is a guideline-classified neurologic emergency [11]. Acute medical treatment of status epilepticus is generally administered intravenously, and warrants hospitalization for stabilization and reduction of the risk for irreversible neuronal damage [12,13].

There are no Food and Drug Administration (FDA) approved treatments for the rapid termination of an ongoing seizure that has not progressed to status epilepticus. Demonstration of a rapid epileptic seizure termination (REST) treatment that acts within minutes of outpatient administration by the patient or a caregiver could advance the care of epilepsy and improve patient outcomes [14,15].

2. Types of seizure emergencies

2.1. Operational seizure classification

The International League Against Epilepsy (ILAE) developed a revised operational classification of seizure types in 2017 according to onset (focal or generalized), and the practical consideration of patient awareness [16]. Focal aware, focal unaware and generalized seizures may be further characterized by motor or nonmotor manifestations, but regardless of the precision of subclassification, any unexpected breakthrough seizure in the setting of previously controlled epilepsy on stable ASM treatment is burdensome to the patient and presents risk for injury [17]. Seizure emergencies may result from any seizure type, but are typically realized when a single episode alludes self-regulatory mechanisms of spontaneous termination, or repetitive seizure episodes cluster temporally [18].

2.2. Categorizing seizure emergencies

Acute repetitive seizures (ARS), although not uniformly accepted, is a clinically defined syndrome characterized by multiple breakthrough seizures (at least two), generally occurring over a period of six to 24 hours in a distinctive pattern [6]. The goal of ARS treatment is to stop the cycle of seizure clusters, delaying or preventing the next seizure, once the pattern is recognized. Seizure clusters may increase the risk of neuronal death, particularly with decreasing interseizure intervals [7]. In contrast, status epilepticus is a clinical state in which a single, unremitting, prolonged seizure will not terminate spontaneously, ultimately leading to neuronal death and brain injury [5]. Documented status epilepticus, defined as greater than five minutes of tonic-clonic convulsions or 10 minutes duration of focal seizure activity, requires urgent intervention with parenteral anticonvulsive therapy and cardiopulmonary support [11,12]. In addition to ARS and status epilepticus, the spectrum of seizure emergencies includes a prolonged seizure that has not yet qualified as progression to status epilepticus, but has failed to self-terminate in a reasonably short time period [18]. How long is “too long” (eg, when is neuronal damage inevitable) to wait for spontaneous termination of a prolonged seizure remains undefined [5], beyond the established recommendation for acute treatment of status epilepticus. To this end, medical management of a single prolonged seizure that has not yet progressed to status epilepticus would require administration within a finite window of time and demonstration of rapid activity (less than five minutes from seizure onset to termination) to offer clinical benefit. Examples of seizure emergencies with current unmet medical need include focal or generalized seizures preceded by an aura, flurries of absence or myoclonic seizures, or prolonged focal and generalized seizures at high risk of progression to status epilepticus.

3. Regulatory approved seizure rescue treatments

3.1. FDA-approved rescue treatments for ARS

There are three FDA-approved medical treatments indicated for management of ARS in the outpatient clinical setting. Each agent was investigated in a relatively homogenous group of epilepsy patients with a documented history of qualifying recurrent seizure cluster episodes.

Diazepam rectal gel (Diastat®) is a rectally administered gel formulation of the benzodiazepine, diazepam, that has been shown to prevent or delay subsequent seizures in patients who experience seizure clusters or ARS. Clinical trials demonstrated that the frequency (per hour) of recurrent seizures was significantly reduced over a period of 12–24 hours following the onset of an identifiable seizure cluster and administration of Diastat versus placebo. Diastat controlled trials report that peak plasma concentration is reached in 90 minutes [8].

Diazepam nasal spray (Valtoco®) is an intranasally administered formulation of the benzodiazepine, diazepam, recently approved for the treatment of ARS in patients with epilepsy. Its clinical efficacy in this setting is based on demonstration of its relative bioavailability compared to diazepam rectal gel (Diastat) in healthy adults. Despite its intranasal administration, Valtoco, like Diastat, reaches peak plasma concentration in 90 minutes [9].

Midazolam nasal spray (Nayzilam®) is an intranasally administered formulation of the benzodiazepine, midazolam, also approved for the treatment of ARS in patients with epilepsy. Like Diastat, it has been shown to prevent or delay subsequent seizures in patients who experience seizure clusters or ARS. Clinical trials demonstrated that more patients treated with Nayzilam after the first cluster were free of seizure cluster activity at 10 minutes, and without recurrence up to 6 hours versus those receiving placebo [19]. Nayzilam reaches peak plasma concentration in 17.3 minutes [10].

3.2. Investigational rescue treatments for ARS

In addition to the FDA-approved rectal and nasally administered benzodiazepines, active studies are investigating a buccal soluble film formulation of diazepam for ARS [20]. Precedent for this administration method has been established by the commercial availability and FDA-approval of clobazam oral film (Sympazan®) as a daily adjunctive ASM for the treatment of seizures associated with Lennox-Gastaut Syndrome [21]. Clobazam oral film has not been systematically developed for the treatment of ARS, but the investigational diazepam buccal film (Libervan®)
was recently shown to have similar percutal and interictal pharmacokinetics and time to peak plasma concentration relative to data reported with the approved rectal gel, Diastat [20]. Further, interim data from a safety, tolerability, and usability study of diazepam buccal film in patients requiring treatment for ARS or cluster seizures has been reported and supports its potential future application in this setting [22].

3.3. FDA-approved rescue treatments for status epilepticus

Injectable benzodiazepines (diazepam, lorazepam) are approved for the acute management of status epilepticus, and they are the currently recommended initial therapy of choice in the emergency treatment setting [13]. The parenteral intravenous administration of potent and short-acting benzodiazepines necessitates close medical monitoring for the occurrence of life-threatening hypotension, respiratory depression requiring intubation, cardiac arrhythmias and other serious side effects. As such, intravenous benzodiazepines do not represent a formulation suitable for use outside of a medically controlled clinical setting. In the prehospital emergency medical services (EMS) treatment setting, paramedic administration of intramuscular midazolam (via autoinjector) has been shown to be noninferior to intravenous lorazepam in termination of status epilepticus, and may be a practical alternative prior to hospital arrival [23]. In practice, every effort to rapidly identify status epilepticus and/or avoid seizure progression to status epilepticus may reduce the resultant risk of hospital admission, and the potential for cardiac and respiratory complications, and brain injury [24].

A comparison of the indications, formulations, and pharmacokinetics of FDA-approved seizure rescue treatments is depicted in Table 1.

3.4. EMA-approved rescue treatment for pediatric prolonged, acute, convulsive seizures

In contrast to the United States, the only ARS rescue treatment approved in both children and adults in the European Union remains Diastat rectal gel. However, in 2011, oromucosal midazolam solution, Buccolam*, became the first pediatric-use marketing authorization approval (PUMA) by the European Medicines Agency (EMA) [25]. The PUMA was granted primarily based on comparable efficacy and safety of oromucosal midazolam to diazepam rectal gel, demonstrating cessation of visible signs of seizures within 10 minutes of administration into the buccal cavity. Maximum plasma concentrations of Buccolam are reached within 30 minutes in children [26].

4. Rapid epileptic seizure termination (REST) treatment

To date, none of the FDA-approved seizure rescue treatments have been systematically studied in epilepsy patients with a history of non-clustering but prolonged breakthrough seizures that, while not routinely progressing to status epilepticus, will evade self-termination for two minutes or longer. Such patients experience a reduced quality of life, adapting activities of daily living to accommodate potential unexpected episodes of physical and/or mental incapacitation. An effective and practical rapid epileptic seizure termination (REST) treatment would require the feasibility of noninvasive, peri- and/or intraictal outpatient administration, portability, ease of use, and pharmacokinetic properties equivalent to parenteral systemic absorption with acute onset anticonvulsive activity [14]. Rectally, intranasally and buccally administered commercially available benzodiazepines may not be suitable candidates for REST treatment due to their inability to reach peak plasma drug concentrations ($T_{\text{max}}$) during the window of opportunity for proactive seizure cessation. However, the pivotal ARS clinical trials evaluating the efficacy and safety of these rescue treatments did not address ongoing seizure termination, but rather the endpoint of prevention or delay of a subsequent seizure, as indicated by absence of seizure activity at 10 minutes and 6 hours post administration [8,10]. Drug absorption by mucosal routes of administration, such as the rectum, nasal or buccal cavity, is likely variable, and the precise onset of anticonvulsive activity is unknown. Thus, whether the seizure threshold is sufficiently elevated with rectally or intranasally administered diazepam or midazolam to enable early seizure termination at plasma levels below $T_{\text{max}}$ remains a research question [27].

Approved treatments for status epilepticus, while generally delivered directly into the systemic circulation with onset of anticonvulsive action in one to three minutes, are not practical options for outpatient REST therapy because of the requirement for parental administration by medically trained professionals and their potential for acute toxicity [13,23].

4.1. Unmet need for REST treatment

Seizure duration varies by seizure type and individual patient anatomic and physiologic factors [28]. Further, a single patient may experience seizures of varying types and duration. However,
despite the seemingly random pattern of breakthrough seizure occurrence, predictability may be learned through historical assessment of seizure onset, seizure location, seizure semiology, and clinical evolution of seizures [29]. As such, patients and caregivers are frequently able to identify predictable breakthrough seizure patterns in epilepsy, including triggers (menses, missed medications, alcohol, sleep deprivation), the presence and nature of auras, the tendency to cluster (e.g., ARS episodes), as well as transitions in awareness and secondary generalization. ARS therapies have significantly advanced the field of seizure rescue treatment, and offer the potential for cognitive and physical recovery by 10 minutes following the first cluster seizure event and successful postictal dosing. However, given that significant seizure activity may occur in the first 10 minutes, and may not be preceded by an identifying cluster, fast-onset treatment options capable of rapidly terminating an evolving seizure if administered by the patient or caregiver at the first sign or symptom could extend rescue treatment to a broader epilepsy population (Fig. 1).

5. Potential REST treatments in clinical development

The clinical development of a viable REST treatment has focused on novel mechanisms for non-invasive delivery of established anticonvulsant medications (e.g., benzodiazepines) into the systemic circulation in concentrations sufficient to rapidly abolish electroencephalogram (EEG) documented epileptiform activity [30]. Literature review and focused internet search suggests that at least three investigational drug delivery systems have the potential for REST treatment, Staccato® alprazolam, Zeneo® midazolam, and midazolam intramuscular autoinjector (Table 2).

### Table 2

| Drug-delivery system description (Sponsor) | Method of administration | Time to REST effect | REST Evidence | Phase of development |
|------------------------------------------|--------------------------|-------------------|---------------|---------------------|
| Staccato® alprazolam (Engage Therapeutics, a wholly owned subsidiary of UCB) | Oral inhalation of heated drug vapor | 30 seconds* | • Abrogation of PPR  
• Seizure termination response > placebo | Phase 3 REST planned |
| Zeneo® midazolam (Crossject) | Needle-free transdermal injection of drug solution to muscle | 3.3 minutes* | • Zeneo injection bioequivalence to IM product delivery  
FDA orphan drug designation for status epilepticus | Phase 3 status epilepticus completed |
| Midazolam autoinjector (Seizalam® Meridian Medical) | Intramuscular autoinjection of drug solution | 3.3 minutes* | • Status epilepticus termination = IV lorazepam | Phase 3 status epilepticus completed |

NR, not reported; PPR, photoparoxysmal response  
*30 second mean time to seizure cessation in phase 2b across all responding seizure types  
† Intramuscular (IM) midazolam median time from active treatment to cessation of convulsions [23,36]
domized, multicenter, placebo-controlled, phase 2b trial evaluated the feasibility of self or caregiver administration, response rate (seizure activity cessation within two minutes after administration and no recurrence of seizure activity within two hours), and safety of two doses of Staccato alprazolam (1-mg and 2-mg) in 116 epilepsy patients with predictable seizure patterns, including generalized seizures starting with a flurry of absence or myoclonic seizures, prolonged focal seizures, or clusters of ≥ two seizures within two hours. Both doses of Staccato alprazolam demonstrated the ability to rapidly terminate seizures in two minutes or less, with response rates statistically superior to placebo (65.8% and 65.8% versus 42.5%, respectively; p = 0.0158 combined treatment arms versus placebo). Among responding patients treated with Staccato alprazolam, median time to seizure cessation was 30 seconds. The most common adverse events included somnolence (14.5%), cough (14.5%), dysgeusia (13.2%), dizziness (5.3%), sedation (2.6%), and throat irritation (2.6%). There were no treatment-related serious adverse events and the majority of reported events were mild in severity [32]. Based on the existing evidence of REST efficacy with Staccato alprazolam, a phase 3 outpatient study in patients with prolonged generalized, focal or cluster seizures is planned.

5.2. Zeneo midazolam

Zeneo (manufactured by Crossject, Dijon France) is a novel, pre-filled needle-free, cartridge-based autoinjector device in development to deliver drugs, in one tenth of a second, through the skin surface to varying subdermal levels (intramuscularly, intradermally, subcutaneously) via gas propulsion and micronozzle array [33]. A human factors study conducted on healthy volunteers suggest the device can be correctly and effectively used by the average adult [34]. Pharmacokinetic studies comparing administration of drug product by the Zeneo delivery system or conventional needle and syringe have met bioequivalence criteria across multisite injections [35]. Zeneo midazolam received FDA Orphan Drug designation in 2018 for the treatment of status epilepticus, facilitating its development as a potential outpatient, REST medication [36]. Clinical data in patients with epilepsy demonstrating abortive efficacy in the treatment of prolonged seizures is awaited.

5.3. Intramuscular midazolam via autoinjector

Proof of concept for the successful clinical application of an intramuscular midazolam autoinjector as a REST treatment for adults and children in status epilepticus under the care of paramedics has been previously demonstrated [23]. Seizalam® (intramuscular midazolam) was recently FDA-approved for healthcare professional administration and treatment of status epilepticus as a medical countermeasure for people exposed to chemicals that cause prolonged seizures, whether those situations are in combat, domestic accidents or international attack [37,38].

6. Conclusion

A substantial minority of patients continue to live with uncontrolled drug-resistant epilepsies. Advances in the acute treatment of breakthrough seizures have been made, but they remain applicable only to ARS/cluster seizures and status epilepticus [8–10,14]. There is clinical, economic, and social burden associated with breakthrough seizures [18]. The introduction of a REST treatment shown to cease epileptiform activity within minutes [15], that may be administered at home by the patient or a caregiver at the first clinical sign of an active or impending seizure, has the potential to significantly improve the lives of patients living with epilepsy. Integration and availability of ARS, status epilepticus, and REST medications may allow an individualized approach to the recommendation for rescue treatment according to patient presentation and type of seizure of emergency.

Finally, given the dearth of knowledge concerning the precise relationship between the pharmacokinetics, pharmacodynamics and anticonvulsant onset of action of fast acting benzodiazepines, there remains opportunity to further investigate the approved intranasally administered ARS treatments, as well as other novel seizure rescue medication formulations (eg, buccal soluble film), as potential REST therapies. Evidence for REST efficacy will require appropriately designed clinical trials evaluating endpoints that accurately measure early termination of an ongoing, prolonged seizure that has not progressed to status epilepticus.

Declaration of Competing Interest

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References

1. Klitgaard H. Epilepsy therapy: anticonvulsants, lessons learned and unmet medical needs. Expert Rev Neurother 2013;13(1):1–4.
2. Wilcox KS, Dixon-Salazar T, Sills GJ, et al. Issues related to the development of new antiseizure treatments. Epilepsia 2013;54(suppl 4):24–34.
3. Tian N, Boring M, Kobau R, Zack MM, Croft JB. Active epilepsy and seizure control in adults — United States, 2013 and 2015. MMWR Mortal Wkly Rep 2018;67(15):437–42.
4. Bonnet LF, Powell GA, Smith CT, et al. Breakthrough seizures — further analysis of the standard versus new antiepileptic drugs (SANAD) study. PLoS ONE. 2017;12(12):e0190015.
5. Dingledine R, Velarh NL, Dudek FE. When and how do seizures kill neurons, and is cell death relevant to epileptogenesis? Adv Exp Med Biol. 2014;813:109–22.
6. Falaye F, Bricaire J, Deveber K, Ghadimi P. Seizure-related death in children: a population-based study. Epilepsia 2017;58(9):1596–601.
7. Hauk S, Shinnar S, Moshe SL, O’Dell C, Legatt AD. The association between seizure clustering and convulsive status epilepticus in patients with intractable complex partial seizures. Epilepsia 1999;40(12):1832–4.
8. Diastat [package insert]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC. 2016.
9. Valtoco [package insert]. San Diego, CA: Neurelis, Inc.: 2020.
10. Nayzilam [package insert]. Smyrna, GA: UCB, Inc.: 2019.
11. Trinka E, Cock H, Hestorff D, et al. A definition of status epilepticus — report of the ILAE task force on classification of status epilepticus. Epilepsia 2015;56(10):1515–23.
12. Trinka E, Kalivianen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure 2017;44:65–73.
13. Clauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsies Curr. 2016;16(1):48–61.
14. French JA, Wechsler R, Geldan MA, et al. Inhalal alprazolam rapidly suppresses epileptic activity in photosensitive patients. Epilepsia 2019;60(8):1602–9.
15. Biton V, French J, Dave H, et al. A two-part, phase 2b efficacy study of Staccato® alprazolam inhaler in patients with epilepsy with a predictable seizure pattern: Topline results from part 2. In Paper presented at: American Academy of Neurology Annual Meeting, April 25-May 1, 2020; Toronto, Canada (meeting canceled due to COVID-19). https://dx.doi.org/10.1016/j.yebeh.2015.06.013.
16. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):522–30.
17. Divino V, Petrella AA, Bollu V, Velez F, Ettinger A, Makin C. Clinical and economic burden of breakthrough seizures. Epilepsy Behav. 2015;51:40–7. https://dx.doi.org/10.1016/j.yebeh.2015.06.013.
18. Maglalang PD, Rautiola D, Siegel RA, Fine JM, Hansson LR, Coles LD, Cloyd JC. Rescue therapies for seizure emergencies: new modes of administration. Epilepsia 2018;59:207–15. https://dx.doi.org/10.1111/epi.14475.
19. Detyniecki K, Van Eijj PJ, Sequeira DJ, Wheelers J, Meng T-C, Pullman WE. Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters—a randomized, double-blind, placebo-
controlled trial. Epilepsia 2019;60(9):1797–808. https://doi.org/10.1111/epi.15159.

[20] Rogawski MA, Heller AH. Diazepam buccal film for the treatment of acute seizures. Epilepsy Behav 2019;101:106537. https://doi.org/10.1016/j.yebeh.2019.106537.

[21] Sympazan [package insert]. Warren, NJ: Aquestive Therapeutics: 2018.

[22] Seinfeld S, Gelfand MA, Heller AH, Buan C, Slatko G. Safety and tolerability associated with chronic intermittent use of diazepam buccal film in adult, adolescent, and pediatric patients with epilepsy. Epilepsia 2020;61(11):2426–34. https://doi.org/10.1111/epi.16996.

[23] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, Barsan W. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366(7):591–600.

[24] Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med 2019;381(22):2103–13.

[25] European Medicines Agency (EMA). European Medicines Agency gives first positive opinion for pediatric-use marketing authorization. EMA. https://www.ema.europa.eu/en/documents/press-release/european-medicines-agency-gives-first-positive-opinion-paediatric-use-marketing-authorisation_en.pdf. Published June 24, 2011. Accessed September 1, 2020.

[26] Buccolam [summary of product characteristics]. Brussels, Belgium: Shire Services BVBA; 2019.

[27] Dhir A, Rogawski MA. Determination of minimal steady-state plasma level of diazepam causing seizure threshold elevation in rats. Epilepsia 2018;59(5):935–44. https://doi.org/10.1111/epi.14069.

[28] Jenssen S, Gracely EJ, Sperling MR. How long do most seizures last? A systematic comparison of seizures recorded in the epilepsy monitoring unit. Epilepsia 2006;47(9):1499–503.

[29] Amengual-Gual M, Sánchez Fernández I, Loddenkemper T. Patterns of epileptic seizure occurrence. Brain Res 2019;1703:3–12.

[30] French JA, Krauss GL, Kastelein D, DiVentura BD, Bagiella E. Effects of marketed antiepileptic drugs and placebo in the human photosensitivity screening protocol. Neurotherapeutics 2014;11(2):412–8.

[31] French JA, Gelland M, Vazquez B, Reich B, Iojjarvi J. Stacatto alprazolam for the treatment of epilepsy. Poster presented at: Park City Epilepsy Meeting; October 6-8, 2019; Park City, UT.

[32] Engage Therapeutics announces phase 2b STATES study of Staccato alprazolam for seizure cessation meets primary endpoint. Engage Therapeutics. https://engagetherapeutics.com/wp-content/uploads/2020/03/Engage-Staccato-Alprazolam-Phase-2b.pdf. Published March 12, 2020. Accessed August 25, 2020.

[33] Bardou M, Luu M, Walker P, Auriel C, Castano X. Efficacy of a novel prefilled, single-use, needle-free device (Zeneo®) in achieving intramuscular agent delivery: an observational study. Adv Ther 2017;34(1):252–60. https://doi.org/10.1007/s12325-016-0452-0.

[34] Allaert F-A, Schueller R, Mabile F, Vincent L, Ferreira C. Human factors study of Zeneo® (needle-free autoinjector) and comparison of different user instruction formats. Panminerva Med 2018;60(2):52–9. https://doi.org/10.23378/S0031-0808.18.01423-7.

[35] Bienvenu B, Aouba A, Gottenbert J-E, Verstuyft C. Single-center, single-dose, open-label, randomized, two-period crossover study on the bioavailability of methotrexate administered using a novel prefilled, needle-free delivery system. Curr Med Res Opin 2017;33(4):605–11. https://doi.org/10.1080/03007995.2016.1263611.

[36] Zeneo® midazolam earns the FDA Orphan Drug designation for the treatment of status epilepticus. Crossject. https://www.crossject.com/sites/default/files/2018-03/Communique%C3%A9%20Or%20DAA%20Anglais.pdf. Published February 14, 2018. Accessed August 25, 2020.

[37] Laney J, Clark M. FDA approval of anti-seizure drug provides a new tool for protecting Americans during a chemical attack. The Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEOCBRND). https://www.jpeocbrnd.osd.mil/news/news-story/2018/10/24/fda-approval-of-anti-seizure-drug-provides-a-new-tool-for-protecting-americans-during-a-chemical-attack. Published October 24, 2018. Accessed August 31, 2020.

[38] Seizalam [package insert]. Lake Forest, IL: Hospira, Inc. (Meridian Medical Technologies): 2018.

[39] Lorazepam Injection [package insert]. Lake Forest, IL: Hospira, Inc. (Meridian Medical Technologies): 2018.

[40] Diazepam Injection, USP [package insert]. Lake Forest, IL: Hospira: 2019.