AN ASSESSMENT OF USABILITY AND DRUG PREPARATION TIME FOR A READY-TO-USE LIQUID GLUCAGON RESCUE PEN

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ABSTRACT

OBJECTIVE: Prompt and reliable intervention is critically important when responding to severe hypoglycemia emergencies. Time-to-treatment and usability of a novel ready-to-use liquid Glucagon Rescue Pen (GRP) was evaluated and compared to current emergency glucagon rescue kits (GEK) which require a complex multi-step reconstitution and administration process.

METHOD: A simulated-use human factors study was conducted with the GRP compared to GEK in 16 participants experienced with GEK, consisting of first responders and caregivers of diabetic patients. A validation study was conducted with 75 adults and adolescent caregivers both experienced and naïve to GEK. In addition, a Phase 3 randomized, controlled, single-blind, crossover clinical trial enrolled 81 adults with T1D compared 1 mg doses of GRP versus GEK, and a comparison of study drug preparation time was performed.

RESULT: In the formative usability study, 14/16 (87.5%) of participants successfully administered a rescue injection using the GRP vs. 5/16 (31.3%) using the GEKs ($p<0.05$). Mean total rescue time was 47.9 seconds with the GRP vs 109.0 seconds with GEKs ($p<0.05$). In the summative validation study, 74/75 (98.7%) of subjects successfully administered the GRP. Overall, there were no patterns of differences between user groups. In the Phase 3 study, drug preparation and administration time was significantly shorter ($p<0.0001$) for GRP (27.3±19.7 seconds) vs GEK (97.2±45.1 seconds).

CONCLUSION: These results demonstrate that the GRP and associated instructional materials can be correctly, safely, and effectively used by the intended user populations. There was a significant difference in drug preparation time in favor of the GRP. These results support the GRP as an alternative to GEKs.

BACKGROUND

Hypoglycemia is highly feared by persons with diabetes and can lead to coma, seizures, and automobile accidents. Currently approved glucagon emergency kits (GEKs) for severe hypoglycemia rescue are based on lyophilized formulations that require manual reconstitution with a vial and syringe at time of use, thus are difficult to administer and not well accepted by users. A novel ready-to-use liquid stable glucagon rescue pen (GRP; Xeris Pharmaceuticals) intended for the treatment of severe hypoglycemia was evaluated in a formative human factors study, summative human factors study, and a randomized controlled trial.

Glucagon Emergency Kit (Standard of Care) has Administration Challenges

- Drug mixed at time of use[1]
- Limited stability in solution[1]
- Nine steps to injection[1]
- 1 ml intramuscular injection[1]
- Many possible failure modes[2]
- Creates fear & anxiety[2]
- Poor user experience[2]
- Requires dosing measurement for pediatric vs. adult dose

[1]GlucaGen® (glucagon [rDNA origin] for injection) Hypokit® Instructions for Use. Novo Nordisk A/S. 25 April 2014.
[2]XSGP-HF02 Study Report. Xeris Pharmaceuticals, Inc. 26 March 2015.

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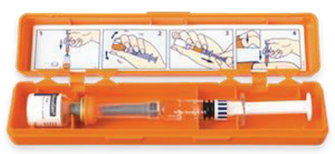

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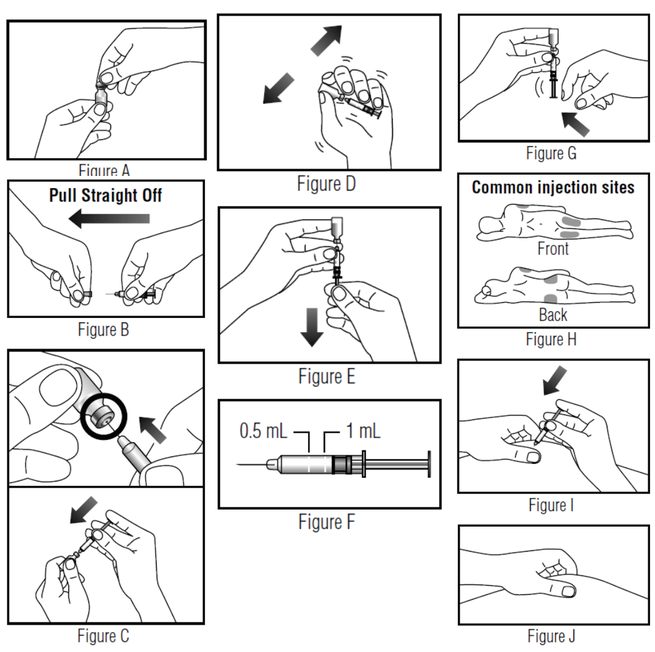
GLUCAGON EMERGENCY KIT INSTRUCTIONS FOR USE*

9-step reconstitution process could be challenging in an emergency situation

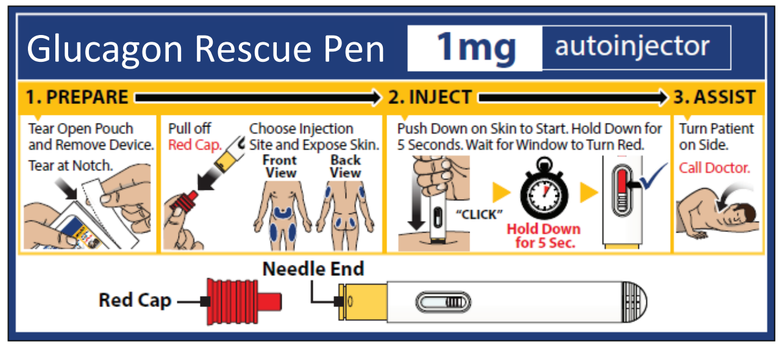
*GlucaGen® (glucagon [rDNA origin] for injection) Hypokit® Instructions for Use. Novo Nordisk A/S. 25 April 2014.



GLUCAGON RESCUE PEN (GRP)

- Pre-mixed solution in SHL Molly auto-injector
- Long-term stability in solution at room temperature[1]
- 0.2 ml subcutaneous injection
- Easy, rapid injection[2]
- Reduces fear & anxiety[2]
- User-friendly[2]

[1]Newswanger B, Ammons S, Phadnis N, et al. Development of a highly stable, nonaqueous glucagon formulation for delivery via infusion pump systems. *J Diabetes Sci Tech.* 2015;9:24–33.
[2]XSGP-HF02 Study Report. Xeris Pharmaceuticals, Inc. 26 March 2015.



OBJECTIVES

The main objectives of these evaluations were to:

- Assess in a formative human factors study the user interaction with both GRP and GEK, to identify potential use errors
- Validate in a summative human factors study whether the GRP injection procedure and associated instructional materials (Dose Label, Packaging, IFU, and Label Guide) can be correctly, safely, and effectively used by the intended user populations (Adult and Pediatric Family/Caregivers and First-Responders)
- Evaluate differences in drug preparation time, between GRP and GEK, in a randomized controlled trial

STUDY DESIGN AND METHODS

FORMATIVE HUMAN FACTORS STUDY

- 16 subjects in a simulated emergency setting, to observe success rates to administer GRP versus GEK
  - 8 glucagon experienced caregivers of PWDs or EMT personnel
  - 8 subjects naïve to glucagon; half were trained, half were untrained

SUMMATIVE HUMAN FACTORS STUDY

TRAINING

A total of 75 first responders and caregivers participated. All First Responders (N=15) received training prior to performing an unsupervised glucagon rescue attempt. All Naïve Pediatric Caregivers (N=15)age 12-17 were trained. In addition, half of the Naïve Adult Caregivers (N=15) received training. All Experienced Caregivers (N=15) and the remaining Naïve Adult Caregivers (N=15) did not receive training prior to performing their unaided rescue attempt.

- Trained participants received a very brief, but representative training which included: an introduction to the device and drug, a verbal walkthrough and each trained participant was given time to read the instructions. They did not get to perform a practice injection with the device
- Untrained participants did not receive any training but instead were given time to familiarize themselves with the device and IFU as they saw fit. As in the real world, these participants did not receive any guidance or instruction as to what to review or how to familiarize themselves with the device

To simulate a realistic decay in knowledge, training (trained) and self-familiarization (untrained) took place during the first study session held one-week prior to the second session which involved the unaided rescue attempt

HF MEASURES

- **Performance Measures:** A successful injection was defined as any injection where the participant performed the correct procedure with the injection device and administered the full dose
- **Behavioral Measures:** Behavioral measures included indices of excessive effort or frustration and verbal comments made by the participant during the study (when applicable)
- **Subjective Measures:** After performing an injection using the injection device, participants were asked to provide subjective feedback on various aspects of the procedure. Participants also provided subjective feedback related to the device, injection procedure, Dose Label, Label Guide, and IFU

PHASE 3 RANDOMIZED CONTROLLED STUDY (NCT #03439072)

- This was a non-inferiority, randomized, controlled, single-blind, 2-treatment, 2-way crossover comparative efficacy and safety study in adult subjects with T1D
- The procedure to evaluate the efficacy of the GRP was performed through an insulin-induced hypoglycemia procedure, used to decrease a subject's plasma glucose to a target <50.0 mg/dL
- After a confirmatory plasma glucose of <50.0 mg/dL was obtained, the subject was treated subcutaneously (SC) in the abdomen with either 1 mg GEK or 1 mg GRP
- Dose preparation time was captured by site personnel by use of a stopwatch and recorded in the EDC in minutes and seconds. Secondarily, it was calculated as the difference in seconds between the Decision to Dose time and the Receiving Glucagon time. A descriptive summary with mean, SD, median, Min, and Max values was provided
- Plasma glucose levels were monitored post-dosing

RESULTS

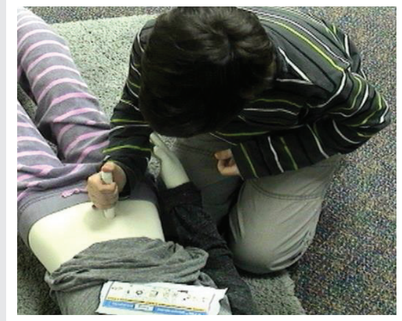
FORMATIVE HUMAN FACTORS STUDY

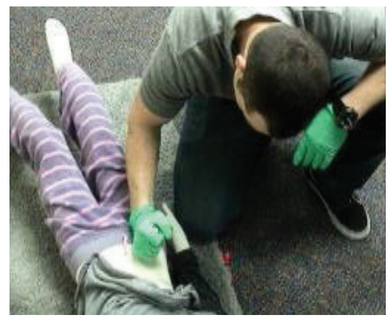
- ***Formative human factors studies have demonstrated that Glucagon Emergency Kit users have very low success rates when attempting to deliver the full dose in a simulated emergency situation***

Sponsor/Product (Date or Venue)	# of Subjects	Glucagon Emergency Kit*		Comparator Product*	
		Trained	Untrained	Trained	Untrained
Biodel – Dual chamber pen (DTM 2015 Presentation)	24	6%	Not reported	87%	88%
Locemia/Lilly – Intranasal powder (EASD 2015 Poster)	16	12.5%	0%	94%	93%
Xeris – Rescue pen (ATTD 2016 Presentation)	16	33%	25%	87.5%	87.5%

*Rate of Success = Complete delivery of dose.

SUMMATIVE HUMAN FACTOR STUDY





- ***Overall, 74/75 participants fully administered the rescue injection using the GRP. The remaining 1 participant lifted the GRP from the injection site too early, but without guidance a repeat attempt was successful***

Successful Task Completion	Trained			Untrained		Overall (N=75)
	First Responders (N=15)	Naïve Adult Caregivers (N=15)	Naïve Pediatric Caregivers (N=15)	Naïve Adult Caregivers (N=15)	Experienced Adult Caregivers (N=15)	
Open and Remove Device from Pouch	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	75/75 (100%)
Remove Cap from Device	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	75/75 (100%)
Inject into the Recommended Injection Site	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	75/75 (100%)
Expose Skin on Site	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	75/75 (100%)
Activate Injection	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	75/75 (100%)
Administer Full Dose	15/15 (100%)	15/15 (100%)	15/15 (100%)	14/15 (93.3%)	15/15 (100%)	74/75 (98.7%)
No Needle Stick	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	15/15 (100%)	75/75 (100%)
All Tasks Complete	15/15 (100%)	15/15 (100%)	15/15 (100%)	14/15 (93.3%)	15/15 (100%)	74/75 (98.7%)

- ***Preparation times for GRP were statistically significantly shorter than for GEK. On average, preparation time for GRP was <30 seconds, compared to >90 seconds for GEK***

PHASE 3 RANDOMIZED CONTROLLED STUDY

	GEK	GRP	P-value
n	78	76	
Drug Preparation and Administration[1], mean ± SD (seconds) Range [low, high] (seconds)	97.2 ± 45.1 [40, 257]	27.3 ± 19.7 [12, 130]	<0.0001[2]
Time to global resolution of neurologic symptoms (minutes ± SD)	15.3 ± 8.0	12.7 ± 6.5	0.02
Resolution of Hypoglycemia Symptoms	100% (78/78)	100% (76/76)	
Global feeling of hypoglycemia improvement pre/post injection	100% (78/78)	100% (76/76)	

SD=standard deviation
[1]Comparison of mean time for preparation of study drug as determined by stopwatch.
[2]Equivalence calculation applied a mixed model for the LS mean difference.

CONCLUSION

The completed results across studies demonstrate that the GRP and associated instructional materials can be correctly, safely, and effectively used by the intended users and use contexts.

- GEK has a low success rate when attempting to deliver the full glucagon dose during simulated emergencies, in multiple formative human factors studies
- 98.7% of both trained and untrained users can successfully administer a full dose of emergency glucagon with GRP, in a summative human factors study
- There was a significant difference in drug preparation time, in favor of the GRP in a Phase 3 clinical study
- There was a significant difference in time to global resolution of hypoglycemia symptoms, in favor of the GRP in a Phase 3 clinical study

In summary, these results support the GRP as a viable alternative to the GEK.

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