CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215143Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 10, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215143
Product Name and Strength:	Succinylcholine Chloride injection, USP, 100 mg/5 mL (20 mg/mL)
Applicant/Sponsor Name:	Hikma Pharmaceuticals USA, Inc.
OSE RCM #:	2020-2182-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD. BCPS
DMEPA 1 Team Leader (Acting):	Murewa Oguntimein, PhD, MHS, CHES, CPH
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on August 6, 2021 for Succinylcholine Chloride Injection, USP. Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Succinylcholine Chloride injection, USP (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 ASSESSMENT OF MATERIALS RECEIVED

The Applicant did not implement our container label recommendations to: -

[a] Getahun, S. URRA and Label Labeling Review for Succinylcholine Chloride (NDA 215143). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 JUL 28. RCM No.: 2020-2127 and 2020-2182.

- include “Usual Dose” statement and
- to present cautionary statement on the luer lock tip cap of the proposed pre-filled syringe.

The Applicant provided the following rationale: -

- *“Due to space constraints, we are unable to include a “Usual Dosage” statement without removing existing critical text on the proposed label. Additionally, there are approved prefilled syringes on the market that do not include a “Usual Dosage” statement due to space constraints. For example, Neostigmine Methylsulfate Injection, NDA 203629.”*

- *“Hikma has been in contact with our luer lock tip cap supplier and they have confirmed it is not possible to emboss the cautionary statement on the luer lock tip cap. To increase awareness of the warning, “Paralyzing Agent” has been included in two different locations and orientations on the syringe label, so it is visible when picking up the syringe either horizontally or holding it vertically to adjust the dose or expel the air bubble.”*

We considered Hikma’s above responses. At this time, we agree with Hikma omitting the “Usual Dose” statement on the container label due to space constraints and we note that the “Usual Dose” statement is included on the carton labeling. Additionally, we agree with Hikma’s presentation of the warning statement “Paralyzing Agent” in two locations on the syringe label for visibility, in lieu of embossing on the luer lock tip cap.

3 CONCLUSION

We acknowledge that the Applicant did not implement all of our previous container label and carton labeling recommendations; however, we find the Applicant’s rationales acceptable. The Applicant has taken reasonable steps to mitigate risk of medication errors. Thus, we have no further recommendations at this time.

APPENDIX A. HIKMA'S REPONSE TO THE AGENCY AND IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 6, 2021

- Hikma's response to the Agency's recommendations received on August 6, 2021 and available at: - \\CDSESUB1\evsprod\nda215143\0018\m1\us\cover-0018.pdf

Container labels

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 08/03/2021

To: Sandy Truong, PharmD, Regulatory Project Manager
Division of Regulatory Operations, Neuroscience (DRO-N)

From: Phillip Williams, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for SUCCINYLCHOLINE CHLORIDE injection, for intravenous or intramuscular use

NDA: 215143

In response to DAAP's consult request dated December 1, 2020, OPDP has reviewed the proposed prescribing information (PI) for SUCCINYLCHOLINE CHLORIDE injection, for intravenous or intramuscular use.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on July 28, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Phillip Williams at (240) 402-3974 or Phillip.Williams@fda.hhs.gov.

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PHILLIP A WILLIAMS
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USE-RELATED RISK ANALYSIS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 28, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215143
Product Name and Strength:	Succinylcholine Chloride injection, USP, 100 mg/5 mL (20 mg/mL)
Device Constituent:	Prefilled syringe
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hikma Pharmaceuticals USA, Inc.
FDA Received Date:	October 1, 2020, November 2, 2020, January 14, 2021, and March 30, 2021
OSE RCM #:	2020-2127 and 2020-2182
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
Human Factors Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Associate Director for Human Factors:	Lolita White, PharmD
DMEPA 1 Division Director:	Irene Z. Chan, PharmD, BCPS

1. REASON FOR REVIEW

This review evaluates the use-related risk analysis (URRA) and labels and labeling submitted for succinylcholine chloride injection 100 mg/5 mL (20 mg/mL) under NDA 215143.

1.1. PRODUCT DESCRIPTION

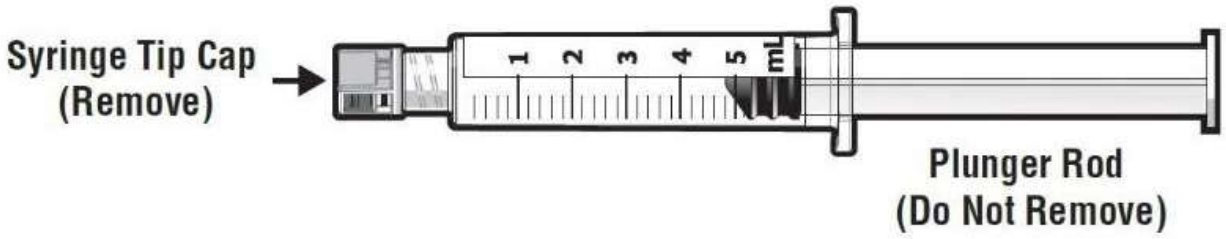
This is a combination product with a proposed pre-filled syringe (PFS) device constituent part containing 100 mg/5 mL succinylcholine chloride and is intended to be administered directly as an intravenous injection or diluted and administered as a continuous infusion as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. The product may be given intramuscularly in cases where a suitable vein is inaccessible. The dose varies based on indication and age of patient. Table 5 in Appendix A contains additional details.

Hikma indicated they proposed the development of succinylcholine chloride injection preservative free PFS:

- To "provide a sterile, ready-to-administer pre-filled syringe product that can be used immediately"
- To streamline medication management from pharmacy to point of care
- To provide cGMP manufactured, preservative -free drug product

Each PFS barrel has a twist off syringe tip cap, luer lock connection that is molded in one piece with the syringe barrel, and a plunger rod. See Figure 1 below. The PFS is sealed in protective overwrap and packaged in a carton; each carton will contain 10 PFS.

Figure 1. Graphic of proposed succinylcholine chloride PFS



2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Use-Related Risk Analysis	E
Comparative Threshold Analysis	F
Information Requests	G
Product Sample, Label and Labeling, Packaging	H

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the use-related risk analysis, comparative analysis, labels and labeling, and total product strength.

3.1. USE-RELATED RISK ANALYSIS (URRA)

We note that customarily, a PFS presentation may be considered "ready to use" by end users. This particular PFS is proposed for varying doses that can be administered directly as an injection as well as for use to create a diluted solution for infusion. In either case, this gives rise to some potential for medication error (e.g., if the full content of the syringe is administered when the dose ordered is less than 100 mg or if the incorrect quantity of syringes are used in creating a diluted solution for infusion. However, we are aware that other approved products exist as PFS presentations that include labeling for varying doses intended for direct administration or use in preparing further diluted intravenous solutions. We considered the risk associated with an underdose or overdose medication error for succinylcholine, and in consultation with DAAP, we determined that this risk may be appropriately managed via labeling. Furthermore, in this particular case, DAAP has noted that the benefits of having an available PFS presentation for succinylcholine outweighs the risk since no such presentation currently exists on the market at this time. We considered this when evaluating the use-related risk analysis (URRA) submitted by Hikma for their proposed product, succinylcholine chloride injection 100 mg/5 mL (20 mg/mL) prefilled syringe.

Based on the information we have at this time, the tasks evaluated in the URRA appear to be comprehensive and appropriate based on what the Applicant proposes for the

design and intended use of this product. Furthermore, we did not identify any additional use-related issues that were not analyzed in the Applicant's URRA.

Based on the Applicant's identified use-related risks for this product, we determined that the Applicant does not need to submit data from a human factor validation study as part of the preapproval submission. However, this does not necessarily mean that the sponsor will not need to conduct testing in accordance with their quality system management plans to meet regulatory requirements under 820.30.

3.2. COMPARATIVE ANALYSES

The Applicant submitted comparative analyses comparing the proposed product to Quelicin (succinylcholine chloride Injection, USP 20 mg/mL) multiple-dose vial presentation approved under NDA 008845 because there are no approved pre-filled syringe presentations of succinylcholine. We did not find this to be an appropriate comparator for bridging/leveraging HF data given the completely different presentations. However, for this particular product, we determined that the URRA and justification were adequate to inform our determination regarding HF data needs (see section above).

3.3. Evaluation of Labels and Labeling

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container label and carton labeling, our rationale for concern, and our proposed recommendation to minimize the risk for medication error.

Table2. Identified Issues and Recommendations for Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
Full Prescribing Information			
1.	Section 3 Dosage Forms and Strengths does not include the appropriate information to facilitate	A description of identifying characteristics is required by 21 CFR 201.57(c)(4)(ii).	We defer to the Office of Pharmaceutical Quality (OPQ) to inform the Applicant to include that the drug product

Table2. Identified Issues and Recommendations for Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	identification of the dosage form.		is a clear, colorless, sterile solution to this section.
2.	The storage statement in Section 16 How Supplied/Storage and Handling does not include units of measurement following the first numbers in the temperature ranges.	Omission of the units of measure, could lead to confusion that may result in deteriorated drug product errors.	Revise the storage information to include the Centigrade symbol (C) following 2° and Fahrenheit symbol (F) following 36°. For example, "Store in refrigerator 2°C to 8°C (36°F to 46°F) …".

Table 3. Identified Issues and Recommendations for Hikma Pharmaceuticals USA, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label			
1.	The statement "WARNING: Paralyzing Agent" is not located directly under the listed strength.	Warning statements should be consistent with class language with other Neuromuscular Blocking Agents (NMBAs) to minimize the risk for confusion.[1]	Add the statement "WARNING: Paralyzing Agent" in red bold font, directly below the product title and the strength and above the route of administration. For example: -

[1] Section 505(o)(4) of FDCA authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes based upon new safety information that FDA becomes aware of after approval of the drug or biological product. On March 7, 2018, the Agency used this authority to request the NDA holders for NMBAs implement labeling changes that provide consistent warning messages in consistent locations on the container labels and carton labeling.

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2.	The red color used as the background color for the drug name and strength reduces the prominence of the recommended class language "WARNING: Paralyzing Agent" statement.	Lack of prominent warning may lead to medication error.	Revise the background color of the drug product, succinylcholine chloride injection, USP, to a different color which does not overlap or look similar to the red class warning statement. In addition, ensure that the color you select does not overlap with any other colors utilized in highlighting the strengths (i.e., white font on black background) to minimize product selection errors.
3.	The format for the expiration date is not defined on the container label.	Clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use on the container label. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and

			month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	The container label does not include a "Usual Dose" statement.	Per 21 CFR 201.55, "…labels for prescription drugs should bear a statement of the recommended or usual dosage."	Include a "Usual Dosage" statement to align with 21 CFR 201.55. To ensure consistency with the prescribing information we recommend stating as "**Recommended Dosage**: See Prescribing Information."
5.	The container label does not inform users to discard any unused contents of the prefilled syringe.	If the entire contents of the prefilled syringe are unintentionally administered or retained, there is risk of overdose or deteriorated drug product errors.	We recommend adding the statement "Discard unused portion" to the container label. For example, "Single dose prefilled syringe – Discard Unused Portion."
6.	The cautionary statement (e.g., "Warning: Paralyzing Agent" or "Paralyzing Agent") present on the ferrule and vial cap of other NMBAs supplied in vials is not present for the proposed product	This important cautionary statement assists health care professionals in clearly identifying neuromuscular blocking agents that produce muscle paralysis (including the muscles associated with breathing), which may cause significant	We recommend you consider presenting this cautionary statement on the luer lock tip cap on the proposed pre-filled syringe.

		patient harm, including death, when used in error.	
Carton Labeling			
1.	Refer to container label recommendations #1-3 and revise accordingly.		
2.	Designated space and format for expiration date is missing on the carton labeling.	Clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date space and format you intend to use on the carton labeling. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate

			the portions of the expiration date.
3.	The statement "Discard Unused Portion" is not prominent as it appears on the back panel of the carton labeling.	Prominence of this statement is important to ensure that the entire contents of the prefilled syringe are not unintentionally administered or retained, thus posing risk of overdose or deteriorated drug product errors.	We recommend relocating the statement "Discard unused portion," to the PDP immediately following the package type term on the carton labeling. For example, "Single dose prefilled syringe – Discard Unused Portion."
4.	The intended location of the machine-readable (2D data matrix barcode) product identifier is not specified.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes. The product identifier contains the NDC, serial number, lot, and expiration date. Additionally, the 2D data matrix barcode should be located in an area that allows sufficient space between it and the existing linear barcode so that both	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).[2] Additionally, we recommend ensuring there is sufficient space between the 2D matrix barcode and the existing linear barcode.

[2] Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers. 2021. Available from: https://www.fda.gov/media/116304/download

		can be read correctly upon scanning.	

4. CONCLUSION AND RECOMMENDATIONS

Based on our review of the URRA of the proposed succinylcholine chloride 100 mg/5mL (20 mg/mL) PFS intended for use by healthcare personnel in a healthcare setting by those skilled in the management of artificial respiration and only when facilities are instantly available for tracheal intubation, we determined that no additional HF data needs to be submitted for the NDA at this time. However, because the proposed product is a combination product, please note that the device constituent should comply with the Quality System regulation, 21 CFR Part 820.

Our evaluation of the proposed succinylcholine chloride prescribing information (PI), container label and carton labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Hikma Pharmaceuticals USA, Inc. so that recommendations are implemented prior to approval of this NDA.

4.1. RESPONSE TO HIKMA

In this specific instance and based on the information we have at this time, we determined that you do not need to submit the results of the human factors (HF) validation study as part of your NDA submission.

However, because the proposed product is a combination product, please note that the device constituent should comply with the Quality System regulation, 21 CFR Part 820. In particular, Section 30, Design Controls, includes requirements relevant to human factors. If further changes are made to the user interface or device constituent part subsequent to this advice, please submit your updated URRA and your determination for HF data requirement for your product.

In addition, our evaluation of your proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3 and we recommend that you implement these recommendations for this NDA 215143. In this particular instance, we determined the recommendations can be implemented without submission of additional HF validation study data in the NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Succinylcholine Chloride PFS that Hikma submitted on October 1, 2020, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Succinylcholine Chloride

Product Name	**Quelicin**	N/A
Initial Approval Date	05/01/1953	N/A
Active Ingredient	Succinylcholine chloride	Succinylcholine chloride
Indication	Adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.	
Route of Administration	Intravenous or intramuscular	
Dosage Form	Injection	
Strength	20 mg/mL	
Dose and Frequency	**Adults:** **For Short Surgical Procedures:** Average dose 0.6 mg/kg given intravenously. Optimum dose will vary among individuals 0.3 mg/kg to 1.1 mg/kg. A 5 mg to 10 mg test dose may be used to determine sensitivity of the patient and the individual recovery time. **For Long Surgical Procedures:** Administered by infusion depends upon the duration of the surgical procedure and the need for muscle relaxation. Average rate for adult ranges between 2.5 mg and 4.3 mg per minute. Intermittent intravenous injections may also be used. Initially 0.3 mg/kg to 1.1 mg/kg may be given initially, followed, at appropriate intervals, by further injections of 0.04 mg/kg to 0.07 mg/kg to maintain the degree of relaxation required. **Pediatrics:** For emergency tracheal intubation or in instances where immediate securing of the airway is necessary, intravenous dose is 2 mg/kg for infants and small pediatric patients; for older pediatric patient and adolescents the dose is 1 mg/kg.	

	Intramuscular Use: If necessary, may be given intramuscularly to infants, older pediatric patients, or adults when a suitable vein is inaccessible. A dose of up to 3 mg/kg to 4 mg/kg may be given, but no more than 150 mg total dose should be administered by this route.	
How Supplied	**Multiple-dose Fliptop Vial:** 200 mg/10 mL (20 mg/mL)	100 mg/5mL (20 mg/mL) – preservative free single dose pre-filled syringe packaged in a carton of 10
Storage	Refrigerator 2°C to 8°C (36 °F to 46 °F). The multiple-dose vials are stable for up to 14 days at room temperature without significant loss of potency.	Refrigerator 2°C to 8°C (36 °F to 46 °F). Single-dose syringes are stable for up to 14 days at room temperature without significant loss of potency.
Container Closure	Fliptop Vials	Pre-Filled syringe

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 30, 2020 and May 4, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, "succinylcholine" and "215143". Our search identified eight (8)[3,4,5,6,7,8,9,10] previous reviews and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX E. USE-RELATED RISK ANALYSIS (URRA)

The use-related risk analysis, received March 30, 2021, can be accessed in the EDR via: \\CDSESUB1\evsprod\nda215143\0010\m3\32-body-data\32p-drug-prod\succinylcholine-chloride-injection\32p2-pharm-dev\pharmaceutical-development-2020-0231-01.pdf

APPENDIX F. COMPARATIVE ANALYSIS

Comparative analysis, received on October 1, 2020, can be accessed in the EDR via: \\CDSESUB1\evsprod\nda215143\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\other-study-reports\5354-other-stud-rep\other-study-reports-2020-0252-00.pdf

APPENDIX G. INFORMATION REQUESTS

[3] Abate, R. Label and Labeling Review for Anectin (Succinylcholine Chloride Injection, USP) (NDA 008453/S-028). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 MAR 14. RCM No.: 2011-498.

[4] Shah, M. Label and Labeling Review for Anectin (Succinylcholine Chloride Injection, USP) (NDA 008453/S-033). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 08. RCM No.: 2017-869.

[5] Shah, M. Memorandum Review of Revised Label and Labeling for Anectin (Succinylcholine Chloride Injection, USP) (NDA 008453/S-033). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 20. RCM No.: 2017-869-1.

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[9] Johnson, C. Suitability Petition Review for Quelicin (Succinylcholine Chloride Injection, USP) (NDA 008845). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 05. RCM No.: 2020-2036.

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We sent an Information Request to the Applicant on December 9, 2020 an information request[11] . In our preliminary review of the "Use-Based Risk Assessment," we noted the step/task "Inspect Syringe" and associated failure modes "Absence of internal particles not checked" and "Proper drug color not checked" include the control "The pre-filled syringe barrel is optically clear, and the label selection and design will ensure that the drug solution can be viewed." However, we noted that the product sample's label was opaque and covers the syringe barrel completely. Therefore, the label on the product samples does not allow users to inspect the prefilled syringe. We asked the Applicant to clarify whether the submitted product samples are representative of intend to market product and to clarify the, inconsistency, if any, between the control for the inspect syringe task in the URRA and product label. The Applicant provided a response on December 14, 2020.

The link to the information request response can be found at: -
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On March 25, 2021 an information request[12] was sent to the applicant noting that the URRA did not have the complete content that are essential for a comprehensive review (i.e. Description of intended users and use environment). As such, we requested for a revised submission for the Applicant to provide a comprehensive URRA along with justification for not submitting HF validation study. The applicant provided a response on March 30, 2021.

The link to the information request response can be found at: -
\\CDSESUB1\evsprod\nda215143\0010\m1\us\cover-0010.pdf

[11] White, T. FDA Communication: NDA 215143 Succinylcholine Chloride Information Request. Silver Spring (MD): FDA, CDER, DAAP (US) 2020 DEC 9. NDA 215143

[12] Patwardhan, S. FDA Communication: NDA 215143 Succinylcholine Chloride Information Request. Silver Spring (MD): FDA, CDER, DAAP (US) 2021 MAR 25. NDA 215143

APPENDIX H. PRODUCT SAMPLE, LABELS AND LABELING, PACKAGING

H.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[13] along with postmarket medication error data, we reviewed the following succinylcholine chloride labels and labeling submitted by Hikma Pharmaceuticals USA, Inc.

- Container label(s) received on October 1, 2020
- Carton labeling received on October 1, 2020
- Prescribing Information (Image not shown) received on January 14, 2021
    - Annotated version available at: \\CDSESUB1\evsprod\nda215143\0006\m1\us\labeling-history-draft-changes.pdf
    - Clean version available at: \\CDSESUB1\evsprod\nda215143\0006\m1\us\draft-labeling-text.pdf

H.2 Label and Labeling Images

Container label

Carton labeling

[13] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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IRENE Z CHAN
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: June 11, 2021 **Date consulted:** December 1, 2020

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

To: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Drug: Succinylcholine Chloride Injection, 100 mg/5 mL (20 mg/mL) pre-filled syringes

NDA: 215143

Applicant: Hikma Pharmaceuticals USA, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Recommendations

Proposed Indication: As adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation

Materials Reviewed:

- October 1, 2020, New NDA 505(b)(2) submission NDA 215143
- December 1, 2020, PLLR consult to DPMH, NDA 215143, DARRTS Reference ID 4709900
- September 24, 2020, DPMH consult, PLLR Quelicin (succinylcholine chloride injection) review, Carrie Ceresa, Pharm D., MPH, Clinical Analyst, DARRTS Reference ID 4675241

Consult Question: "DAAP is requesting an MHT consult to assist us in reviewing the labeling for the PLLR format."

INTRODUCTION AND BACKGROUND

On October 1, 2020, Hikma Pharmaceuticals USA Inc., submitted an original 505(b)(2) application for NDA 215143 (succinylcholine chloride injection) pre-filled syringes. The NDA 215143 submission is based on the reference listed drug Quelicin (succinylcholine chloride) injection, multiple dose vials under NDA 8845.

The reader is referred to the September 24, 2020, DPMH review for succinylcholine NDA 08845 for a detailed review regarding succinylcholine exposure during pregnancy, lactation and effects on females and males of reproductive potential.

Table 1: Succinylcholine Injection Drug Characteristics[1]

Original Approval	Original Succinylcholine Injection approval May 1, 1953
Mechanism of Action	Succinylcholine is a depolarizing skeletal muscle relaxant that combines with the cholinergic receptors of the motor end place to product depolarization; neuromuscular transmission is inhibited so long as adequate concentration of succinylcholine remains at the receptor site and with single administration causes rapid flaccid paralysis with single administration lasting 4 to 6 minutes
Dose and Administration	Individualized and determined by the clinician
Molecular Weight	361.31 Daltons
Warnings and Precautions	Anaphylaxis, risk of death due to medication errors, hyperkalemia, malignant hyperthermia, bradycardia, increase in intraocular pressure
Adverse Reactions	Severe allergic reactions (anaphylactic and anaphylactoid reactions); cardiac arrest, malignant hyperthermia, arrhythmias, bradycardia, tachycardia, hypertension, hypotension, hyperkalemia, prolonged respiratory depression or apnea, increased intraocular pressure, muscle fasciculation, jaw rigidity, postoperative muscle pain, rhabdomyolysis with possible myoglobinuric acute renal failure, excessive salivation and rash

Current State of RLD Labeling

- The voluntary supplement for Quelicin for the conversion to the PLR/PLLR labeling has not yet been approved.
    - The previous Quelicin labeling approved on July 26, 2018, removed the pregnancy category, added a Risk Summary, general boilerplate language for all pregnancy sections and nonteratogenic effects were converted to Clinical Considerations.
- Animal reproduction studies have not been performed.

[1] Approved succinylcholine labeling

- There are no human data with regards to succinylcholine and exposure during pregnancy.
- There is a Clinical Considerations section that discusses plasma cholinesterase levels during pregnancy and postpartum and the risk of increased sensitivity (prolonged apnea) to succinylcholine when given to nonpregnant women. Patients with atypical cholinesterase can experience an even greater duration of neuromuscular blockade. This effect is discussed in more detail below in the review section.
- There is also a Labor and Delivery subsection with regards to the use of succinylcholine to provide muscle relaxation during caesarean delivery.
- There is no information in the current labeling with regards to succinylcholine and breastfeeding.

DATA REVIEW

PREGNANCY

Pregnancy and Anesthesia: Muscle Relaxation during Surgery or Mechanical Ventilation

- Approximately 0.5 - 2% of pregnant women go through surgery for non-obstetric procedures each year which most commonly include appendicitis, cholecystitis, trauma, and maternal malignancies.[2,3,4,5]
- Risks during surgery in pregnant women include fetal loss and premature delivery. An overall miscarriage rate after surgery is reported to be 5.8% (10.5% during the first trimester).[6,7] One of the goals during surgery in a pregnant women is to provide safe anesthesia for mother and fetus.[7]
- Physiological changes in pregnancy include changes in the following body systems: cardiovascular, respiratory, CNS, hematological, gastrointestinal and renal. See Table 2 below for physiological changes and corresponding anesthetic implications.[2]
    - When a pregnant woman is in a supine position, functional residual capacity is decreased by 20% or more; therefore, when periods of apnea occur, pregnant women are more at risk for hypoxia. Endotracheal intubation is also more difficult due to anatomical changes to a pregnant women's airway.[7]
    - Reductions in anesthesia requirements of anesthetic agents in pregnant women are required due to increased sensitivity to inhalation and inhalation anesthetics from hormonal changes and an enlarged uterus.[7]

[2] Nejdlova M and T Johnson. Anesthesia for non-obstetric procedures during pregnancy. Continuing Education in Anesthesia, Critical Care & Pain. 2012;12,203-206.
[3] Crowhurst JA. Anesthesia for non-obstetric surgery during pregnancy. Acta Anaesthesiol Belg. 2002;53(4), 295-7.
[4] Kuczkowski K. Nonobstetric surgery during pregnancy:what are the risks of anesthesia. Obstet Gynecol Surg. 2004, 59(1), 52-6.
[5] Allaert SEG, Carlier SPK, Weyne LPG, et al. First trimester anesthesia exposure and fetal outcome. A review. Acta Anaesthesiol Belg. 2007; 119-23.
[6] Cohen-Kerem R, Railton C, Oren D, et al. Pregnancy outcome following non-obstetric surgical intervention. Am J Surg. 2005;190(3), 467-73.
[7] Van De Velde M and F De Buck. Anesthesia for non-obstetric surgery in the pregnant patient. Minerva Anesthesiol. 2007; 73(4), 235-40.

- Succinylcholine is the muscle relaxant of choice for rapid sequence intubation in pregnant women as the duration of action is not affected by pregnancy.[7]

Table 2. Physiological changes during pregnancy and anesthetic implications. (copied from Nejdlova M and T Johnson, 2012, corresponds to Table 1 page 204)[2]

System	Physiological change	Anaesthetic implications
Cardiovascular	↑ CO up to 50%	
	↑ Uterine perfusion to 10% of CO	Uterine perfusion not autoregulated
	↓ SVR, ↓ PVR, ↓ AP	Hypotension common under regional and general anaesthesia
	Aortocaval compression from 13 weeks	Supine hypotensive syndrome requires left lateral tilt
Respiratory	↑ Minute ventilation	Faster inhalation induction
	Respiratory alkalosis (Pa_{CO_2} 3.7–4.2 kPa)	Maintain Pa_{CO_2} at normal pregnancy levels
	↓ ERV, ↓RV, ↓ FRC	
	↑ V/Q mismatch	
	↑ Oxygen consumption	
	Upward displacement of diaphragm	Potential hypoxaemia in the supine and Trendelenburg positions
	↑ Thoracic diameter	Breathing more diaphragmatic than thoracic
	Mucosal oedema	Difficult laryngoscopy and intubation; bleeding during attempts
CNS	↑ Epidural vein engorgement	Bloody tap more common
	↓ Epidural space volume	More extensive local anaesthetic spread
	↑ Sensitivity to opioids and sedatives	
Haematological	↑ Red cell volume 30%, ↑ WCC	
	↑ Plasma volume 50%	Dilutional anaemia
	↑ Coagulation factors	Thromboembolic complications (DVT prophylaxis)
	↓ Albumin and colloid osmotic pressure	Oedema, decreased protein binding of drugs
Gastrointestinal	↑ Intragastric pressure	↑ Aspiration risk
	↓ Barrier pressure	Antacid prophylaxis, RSI after 18 weeks gestation
Renal	↑ Renal plasma flow, ↑ GFR	Normal urea and creatinine may mask impaired renal function
	↓ Reabsorptive capacity	Glycosuria and proteinuria

*Cardiac output (CO), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), arterial pressure (AP), expiratory reserve volume (ERV), residual volume (RV), functional residual capacity (FRC), ventilation/perfusion (V/Q), minimum alveolar concentration (MAC), white cell count (WCC), glomerular filtration rate (GFR)

Nonclinical Experience

Animal reproduction studies with succinylcholine have not been conducted.

Review of Literature

Applicant's Review of Literature

A summary of the relevant literature submitted by the applicant not yet reviewed in the previous DPMH succinylcholine review can be found in Appendix A. The applicant concluded that after review of the literature there are no new relevant published data with regards to succinylcholine exposure during pregnancy and structural abnormalities or embryo-fetal/infant mortality.

DPMH's Review of Literature
DPMH conducted an updated search of published literature since the previous 2020 DPMH review using PubMed and Embase regarding succinylcholine exposure during pregnancy using the following search terms, "succinylcholine and fetal malformations," "succinylcholine and spontaneous abortion and miscarriage," "succinylcholine and embryo-fetotoxicity." In addition to the applicant's review of literature, no new safety concerns were revealed since the previous DPMH review of succinylcholine. The reader is referred to previous DPMH review for information regarding succinylcholine and use during pregnancy.

Reviewer comment:
The applicant conducted an adequate review of the literature with regards to succinylcholine and exposure during pregnancy. See the Discussion/Conclusions section below for DPMH's conclusion summary.

LACTATION
Nonclinical Experience
Animal reproduction studies with succinylcholine have not been conducted.

Applicant's Review of Literature
The applicant conducted a review of published literature with regards to lactation and succinylcholine. The applicant concluded that no publications were found regarding succinylcholine levels in breastfed infants. In addition, the applicant concluded that because succinylcholine is rapidly hydrolyzed in maternal plasma and has a short half-life of 3 to 5 minutes, it is unlikely to be excreted into milk or absorbed orally by the infant.

DPMH's Review of Literature
DPMH conducted an updated search of published literature since the previous 2020 DPMH review. No new data were found since the previous review. The reader is referred to the previous DPMH succinylcholine review for information regarding the literature search with regards to succinylcholine exposure and lactation.

Reviewer comment:
The applicant conducted an adequate review of the literature with regards to succinylcholine and use during lactation. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
No animal fertility studies have been conducted to evaluate the potential impact of succinylcholine on fertility. The applicant and DPMH conducted a review of literature with regards to succinylcholine and effects on fertility in males and females of reproductive potential. There are no data on the effects of succinylcholine on fertility and no known drug-drug interactions with succinylcholine and hormonal contraception.

DISCUSSION/CONCLUSIONS
The literature and data reviewed for this review did not reveal any new safety concerns since the previous DPMH review for succinylcholine exposure in pregnancy, lactation and females and males of reproductive potential. DPMH recommends that the succinylcholine injection labeling is updated to reflect the DPMH recommendations from the previous DPMH succinylcholine review with a few minor edits shown below.

RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 in succinylcholine labeling for compliance with the PLLR (see below). DPMH refers to the final NDA 215143 action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

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Appendix A.

Table 1. Literature submitted by the applicant regarding exposure to succinylcholine during pregnancy.

Publication	**Study Design**	**Maternal/Fetal Exposure**	**Outcome/ Conclusion**
Felton DJ (1966)[8]	A study of five women undergoing cesarean birth to evaluate the effect of suxamethonium on uterine activity	Suxamethonium 50-60 mg IV initially and anesthesia was maintained after endotracheal intubation by intermittent injections of suxamethonium.	An increase was observed in uterine activity such that a greater frequency of contractions and raising of uterine tonus was observed. The authors concluded that this was an oxytocic effect due to suxamethonium.
Leighton BL (1986)[9]	Pharmacodynamic study of succinylcholine in peripartum patents.	Authors compared serum cholinesterase activity and recovery from succinylcholine, 1 mg/kg in nonpregnant women with or without oral contraceptive use and in-term pregnant and postpartum patients.	Serum cholinesterase activity was lower in both term-pregnant and postpartum patients than in nonpregnant patients not taking oral contraceptives. Cholinesterase activity in postpartum patients was also significantly lower than in nonpregnant patients taking oral contraceptives. Authors believe that this could be due to increased volume of distribution of succinylcholine at term.
Davis L (1977)[10]	Conducted a review of cholinesterase activity in pregnancy	N/A	Conclusion suggests that there is a decrease in plasma cholinesterase activity in about 20% of women in the first trimester and this level is maintained until delivery. Two to four days after delivery there is a further 33% reduction in activity which appear to return to pre-pregnancy levels at approximately 6 weeks postpartum.
Robertson GS (1966)[11]	Conducted a review of serum cholinesterase changes during pregnancy; 149 patients	N/A	Authors conclude there is a diminution of serum cholinesterase activity compared with non-pregnant women of child-bearing age that begins after 10 weeks gestation.
Evans RT (1980)[12]	Measurement of cholinesterase activity in 941 pregnant women	N/A	A rapid fall was observed during the first trimester to a level which did not change significantly throughout pregnancy. The conclusion was that

[8] Felton DJ. The effect of suxamethonium chloride on uterine activity. The Lancet. 1966; 1(7442):852-854.
[9] Leighton BL, Cheek TG, Gross JB, et al. Succinylcholine pharmacodynamics in peripartum patients. Anesthesiology. 1986;64(2):202-205.
[10] Davis L, Robertson GS.Britten JJ, Morgan M. Cholinesterase. Its significance in anaesthetic practice. Anaesthesia. 1997;52(3):244-260.
[11] Robertson GS. Serum cholinesterase deficiency. II. Pregnancy. Br J Anaesth. 1966;38(5):361-369.
[12] Evans RT, Wroe JM. Plasma cholinesterase changes during pregnancy. Their interpretation as a cause of suxamethonium-induced apnoea. Anaesthesia. 1980;35(7):651-654.

Publication	Study Design	Maternal/Fetal Exposure	Outcome/ Conclusion
	throughout 40 weeks gestation		cholinesterase activity in serum is significantly lower in pregnant women than non-pregnant controls.
Nejdlova M (2012)[13]	Literature review of neuromuscular blocking agents	N/A	Plasma cholinesterase levels were reduced by up to 35% in pregnant women suggesting the volume of distribution may contribute to the lower level.
Cherala (1989)[14]	Case report 34-year old female	During cesarean delivery was given thiamylal 200 mg and succinylcholine 100 mg following IV administration	One day after delivery the infant had cholinesterase levels of 410 U/I (normal 2436-4872). Authors suggest that a similar depression of cholinesterase activity that occurs in pregnant women also occurs in the newborn.
Owens WD (1975)[15]	Case report newborn	Hypoventilation following administration of succinylcholine to the mother; patient received 0.5 mg of atropine before induction; was preoxygenated for 5 minutes and induced rapidly with 150 mg of sodium thiopental and 80 mg of succinylcholine IV; extra dose of 60 mg of succinylcholine by slow IV infusion between time of intubation and delivery	Neonate had an Apgar score of 7 at 1 minute with hypoventilation, decreased tonus, and decreased motion to reflex stimulation; respiratory rate 60 to 80 min and small respiratory excursions. Ventilatory support given to newborn for 10 minutes until muscle tone and respiration recovered.
Frawley (1994)[16]	Case report premature neonate	Prolonged apnea developed in neonate due to suxamethonium; 20 hours of prolonged apnea in a 3-week old infant born at 33 weeks' gestation following suxamethonium administration	Authors concluded that the incidence of abnormal pseudocholinesterase in neonates is unknown and the duration of suxamethonium in neonates homozygous for abnormal enzymes is not well understood.
Moya F (1961)[17]	Study of placental remission of succinylcholine; investigation of maternal venous and umbilical cord blood concentration	14 cesarean sections a single dose 100 mg of succinylcholine was administered by IV infusion throughout induction.	Succinylcholine when given in usual clinical doses was not found in the umbilical vein blood in detectable quantities and it was concluded that it does not cross the placenta and the infants did not appear affected.

[13] 15Nejdlova M, Johnson T. Anaesthesia for non-obstetric procedures during pregnancy. Continuing Education in Anaesthesia Critical Care & Pain. 2012; 12(4):203-206.
[14] Cherala SR, Eddie DN, Sechzer PH. Placental transfer of succinylcholine causing transient respiratory depression in the newborn. Anaesth Intensive Care. 1989;17(2):202-204.
[15] Owens WD, Zeitlin GL. Hypoventilation in a newborn following administration of succinylcholine to the mother: a case report. Anesth Analg. 1975;54(1):38-40.
[16] Frawley GP, Carden JR. Suxamethonium-induced prolonged apnoea in a premature neonate. Anaesth Intensive Care. 1994;22(2):192-194.
[17] Moya F, Kvisselgaard N. The placental transmission of succinylcholine. Anesthesiology. 1961;22:1-6.

Publication	Study Design	Maternal/Fetal Exposure	Outcome/ Conclusion
	following clinical doses of succinylcholine		
Pacifici GM (1995)[18]	Study of suxamethonium chloride 100 to 600 mg infused in 14 pregnancies at term.	100 to 600 mg suxamethonium	Blood levels were measurable in 5 out of the 14 mothers (range 1.5 and 3.2 mg/L) and not detected in the cord blood of any neonates.
Kvisselgaard (1961)[19]	Measure of plasma concentrations of succinylcholine from 13 mothers and babies after vaginal delivery who received succinylcholine in large bolus dose	Succinylcholine between 200 and 500 mg (2.86 to 7.70 mg/kg).	Doses of over 300 mg of succinylcholine were needed before small (1 to 2 mcg/ml of serum) detected amounts in umbilical vein blood. Authors concluded that succinylcholine could pass the placenta only at doses 3 to 6 times the usual clinical dose.

[18] Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. Clin Pharmacokinet. 1995;28(3):235-269.
[19] Kvisselgaard N, Moya F. Investigation of placental thresholds to succinylcholine. Anesthesiology. 1961;22:7-10.

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