CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215143Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review

Date	August 20, 2021
From	Renee Petit-Scott, MD; Alla Bazini, MD; Rigoberto Roca, MD
NDA#	215143
Applicant	Hikma Pharmaceuticals USA, Inc.
Date of Submission	October 1, 2020
PDUFA Goal Date	August 21, 2021
Proprietary Name	N/A
Established or Proper Name	Succinylcholine Chloride
Dosage Form	Intravenous and intramuscular injection
Applicant Proposed Indication	Succinylcholine chloride is indicated as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation
Applicant Proposed Dosing Regimen	Adults: • For short surgical procedures: 0.6 mg/kg injection given intravenously • For long surgical procedures: 2.5 and 4.3 mg per minute Pediatrics: • For tracheal intubation in infants: 2 mg/kg • For tracheal intubation in older pediatric patients, and adolescents: 1 mg/kg
Regulatory Action	Approval
Approved Indication	Succinylcholine Chloride Injection is a depolarizing neuromuscular blocker indicated in adults and pediatric patients: • as an adjunct to general anesthesia • to facilitate tracheal intubation • to provide skeletal muscle relaxation during surgery or mechanical ventilation
Approved Dosing Regimen	Intravenous Use in Adults: • For short surgical procedures: 0.6 mg/kg injection given intravenously • For long surgical procedures: 0.5 mg to 10 mg per minute, average rate 2.5 mg to 4.3 mg per minute • Intermittent intravenous injection: 0.3 to 1.1 mg/kg initially, followed by 0.04 to 0.07 mg/kg for maintenance

	Intravenous Use in Pediatric Patients: • For emergency tracheal intubation – in infants and other small pediatric patients: 2 mg/kg – in older pediatric patients and adolescents: 1 mg/kg Intramuscular Use in Adults and Pediatric Patients: • 3 to 4 mg/kg for infants, older pediatric patients, or adults • Total dose administered should not exceed 150 mg

OND Action Package included reviews by the following:	
Clinical Pharmacology Review Team	Deep Kwatra, PhD.; Yun Xu, PhD
Division of Pediatric and Maternal Health	Carrie Ceresa, PharmD, MPH; Miriam Dinatale, DO
Pharmacology-Toxicology Review Team	Imran Khan, PhD.; Jay Chang, PhD.; R. Daniel Mellon, PhD
Office of Prescription Drug Promotion (OPDP)	Phillip Williams, PharmD; Sam Skariah, PharmD
Office of Product Quality Review Team Drug Substance Drug Product Process/Facilities Microbiology Biopharmaceutics	Acting Team Leader - Valerie Amspacher, PhD Katie Duncan, PhD.; Donna Christner, PhD Jizhou Want, PhD.; Julia Pinto, PhD Khalid Khan, PhD.; Frank Wackes, PhD Kathik Krishnan, PhD.; Yeissa Chabrier-Rosello, PhD Kamrun Nahar, PhD.; Hansong Chen, PhD
Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis	Sofanit Getahun, PhD.; Millie Shah, PhD

1. Benefit-Risk Assessment

Hikma Pharmaceuticals USA Incorporated (Hikma) submitted this new drug application (NDA) through the 505(b)(2) marketing pathway with reliance on the Agency's previous findings of safety and effectiveness for the listed drug, Quelicin™ (succinylcholine chloride, NDA 008845). Quelicin was approved in 1953, and is indicated as an adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Hikma developed a preservative-free formulation of succinylcholine chloride (succinylchloride) in a 5 mL prefilled syringe. Their rationale for developing this presentation was to provide a sterile, ready-to-administer product that can be used immediately; to provide a product that streamlines the medication management from pharmacy to point of care; and to provide a cGMP manufactured, preservative-free drug product.[1] The Applicant currently markets an ANDA product, 213229, succinylcholine chloride injection (preserved) in vials.

The benefits of this presentation of succinylcholine include the following:

- Commonly administered strength, 20 mg/mL
- Ready and easy to use 5 mL syringe
- Preservative-free
- Additional succinylcholine product available

[1] Cover letter, Original NDA, received October 1, 2020.

- Adequate dose for most patients (5 mL or less of succinylcholine provides adequate muscle relaxation for either short procedures or endotracheal intubation for most patients)
- Decreased risks of:
  - medication error due to lack of need for individual practitioner syringe labeling
  - microbial contamination due to lack of withdrawing medication from a vial
  - errors and contamination associated with compounding pharmacies

The risks and drawbacks of this presentation of succinylcholine include the following:

- Those associated with administration of succinylcholine, including but not limited to acute rhabdomyolysis, hyperkalemia, ventricular dysrhythmias, cardiac arrest, and death in pediatric patients
- Technical issues with the syringe presentation, including poor connectivity to an intravenous catheter port, and medication administration
- Smaller volume, lower strength, of medication compared to listed drug vials (i.e., 100 mg/5 mL versus 200 mg/10 mL)
- Impractical for continuous intravenous infusion
- Smaller pediatric patients may require smaller administration volumes, which may require transfer to a lower volume syringe (i.e., 1 or 3 mL)
- Patients weighing more than 90 kg may require more than one syringe for adequate muscle relaxation, which may be cumbersome particularly in an emergency situation
- Intramuscular use may require more than one syringe, which may be cumbersome in an emergency situation

The Division concludes that the benefits of succinylcholine chloride, preservative-free in prefilled syringes, outweigh the risks. The most notable benefits include the ease of use of the 5 mL prefilled syringe, which is likely to provide adequate dosing for the majority of surgical, trauma, or ER patients requiring muscle relaxation and intubation. Additionally, approval of this application would provide an additional succinylcholine product available to clinicians, which given the history of drug shortages is an important consideration.

There do not appear to be any new risks associated with this succinylcholine presentation that would preclude approval.

2. Background

This document will serve as the Cross-Discipline Team Leader and the Division Director Summary Review of NDA 215143 for the decision on regulatory action for the proposed product, Succinylcholine Chloride Injection, Preservative-Free, 100 mg/5 mL (20 mg/mL) in prefilled syringes. Hikma submitted NDA 215143 on October 1, 2020, through the 505(b)(2) marketing pathway with reliance on the Agency's previous findings of safety and effectiveness for Quelicin (NDA 008845), originally approved in 1953. There were no interactions with the Applicant regarding their proposed drug product prior to submission of their NDA.

Succinylcholine is a depolarizing neuromuscular blocking drug, currently the only FDA approved drug in its class, which binds post-synaptic cholinergic (nicotinic) receptors, similar

to acetylcholine (ACh), in the neuromuscular junction. Succinylcholine is hydrolyzed more slowly in the junction compared to ACh, resulting in sustained depolarization, observed initially as muscle fasciculations, thereby preventing further binding and stimulation by ACh. Muscle paralysis quickly follows observed fasciculations. There is no known reversal agent for succinylcholine and, administration of a cholinesterase inhibitor such as neostigmine will potentiate the depolarization neuromuscular block, commonly referred to as a Phase I block. Continuous or repeated administration of succinylcholine can result in a Phase II, or desensitization neuromuscular block. The action of succinylcholine is terminated by diffusion into the extracellular space, and metabolism to inactive metabolites via plasma (pseudo) cholinesterases, located outside the neuromuscular junction.

The Applicant did not conduct any original clinical studies, including safety, efficacy, or QT studies, and submitted a Request for Waiver of In Vivo Bioavailability Studies (biowaiver), which was determined by the biopharmaceutics and clinical pharmacology review teams to be acceptable. The submitted label was consistent with the requirements of the Physician Labeling Rule; however, because the listed drug's label had not been converted to adhere to the rule requirements at the time of NDA filing, the Applicant's draft label included substantial rearranging and reformatting of information. The Applicant submitted a review and summary of all available nonclinical and clinical information to support all edits to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling.

3. Product Quality

The following information is adapted from the review completed by the teams in the Office of Product Quality.

Product Overview

Hikma's proposed drug product is clear, colorless succinylcholine chloride in a 5 mL colorless syringe for intravenous or intramuscular administration. It is packaged as a 5 mL fill (20 mg/mL concentration) in a 5 mL single dose prefilled (b) (4) syringe barrel and sealed with a (b) (4) closure, and a subsequent (b) (4) plunger rod. A shelf-life of 15 months is acceptable when stored refrigerated (2-8˚C), and up to 14 days when stored at controlled room temperature.

Quality Assessment Overview

Drug Substance

The drug substance CMC information for succinylcholine chloride is cross referenced to DMF (b) (4) The Applicant provided a brief description of the general properties of the drug substance and impurities, which are in accordance with the USP and the drug substance manufacturer. The drug substance manufacturer proposes a retest period of (b) (4) months on the drug substance from the supplier. The details of the testing performed and method verification were provided by the Applicant. The information provided for the drug substance was adequate and the CMC review team had no concerns.

Drug Product

The release specifications of the drug product have been adequately controlled, and the suitability of the container closure system (prefilled syringe) was validated by long-term and accelerated stability and photostability studies, and extractables and leachables studies. A complete extractable profile for the container closure system was provided, and represents the worst case scenario for leachables. The Applicant proposed wider acceptance criteria for the stability specifications of certain impurities, which have been justified by the inhouse data trend and the listed drug impurity profiles. Both upright and horizontal syringe positions have been evaluated. The Applicant proposed a shelf life of 15 months for the drug product at refrigerated temperature based on the statistical evaluations. Supporting stability data of Photostability Study, Freeze-Thaw Study, Fourteen Day Room Temperature Study and In-use/diluent studies have been provided to support the stability profiles for use and shipping. The information provided for the drug product was adequate and the CMC review team had no concerns.

Manufacturing

The manufacturing process consists of (b) (4) (b) (4) (b) (4) The manufacturing instructions, manufacturing equipment, environmental controls, in-process controls and controls for the (b) (4) are adequate to support manufacture of succinylcholine chloride injection in prefilled syringes for this application. The information provided for the manufacturing process was adequate and the CMC review team had no concerns.

Refer to the review completed by the OPQ team for additional information regarding drug product manufacturing, drug substance manufacturing, and test facilities.

Biopharmaceutics

The Applicant requested a biowaiver for the proposed product in accordance with 21 CFR 320.22(b)(1). The only difference between the listed drug and the proposed drug is lack of a preservative agent (methylparaben and propylparaben). The Applicant provided a side-by-side comparison of the physicochemical properties of the listed drug and the proposed drug product. The physicochemical property data are comparable and the biowaiver can be granted. The biopharmaceutics review team had no additional concerns.

Microbiology

(b) (4) have been adequately validated. The Applicant has met the regulatory expectations with regard to the test methods, acceptance criteria, and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release. The information provided for sterility testing and (b) (4) procedures was adequate and the microbiology review team had no concerns.

During the labeling review, the clinical team questioned whether the proposed product could be classified as multi-dose use in a single patient (single use) or single dose. Single use

classification allows products to be administered for more than one dose in a single patient, a scenario that happens commonly in the operating room. This classification, however, requires additional microbiology data that the Applicant had not submitted. Therefore, single dose information is included in the product labeling, indicating that when additional succinylcholine is required, a new prefilled syringe is needed for each administration, even under circumstances of residual drug in a previously used syringe for the same patient.

Based on drug substance, drug product, process/manufacturing, biopharmaceutics and microbiology reviews, the OPQ review team has no additional concerns and recommends approval of this application. The Division concurs.

4. Nonclinical Pharmacology/Toxicology

The following information is adapted from the review completed by the pharmacology/toxicology review team.

No new nonclinical toxicological studies were submitted to support this NDA. Drug substance impurities and drug product degradants were either within specification limits according to the ICH Q3A(R2) and Q3B(R2) guidances, respectively, or the levels can be justified to be safe for human use based on information for the approved referenced product (i.e., within the same range).

Extractables and leachables studies were performed to justify the safety of the proposed container closure system, which consists of a 5 mL prefilled plastic syringe with plastic tip cap, plunger stopper, plunger rod, and adhesive label. Although numerous potential leachables, including elemental impurities, were identified in the extractables study with the container closure system, only two organic compounds (b) (4) (b) (4) and 2 USP <232> elemental leachables (b) (4) were identified in the long term stability sample at or above the Applicant's reporting limit. The levels of (b) (4) are not of safety concern for humans based on permissible daily exposure levels being higher than those resulting from administration of the drug product at the maximum recommended daily dose (i.e., 600 mg/day).

Although there are no toxicological data for (b) (4) to determine the permissible daily exposure (PDE) for this leachable impurity, the quantitative structure-activity relationship (QSAR) analyses completed by the Applicant and the review team conclude it is non-mutagenic. Moreover, analysis of the toxicological data available for the surrogate compounds for (b) (4) provide PDEs that indicate the maximum daily intake for this impurity, (b) (4) mg/day, does not present a safety concern for humans during parenteral administration of the drug product. The pharmacology/toxicology review team has no safety concerns regarding potential leachables arising from the container closure system.

The Applicant provided a literature review that included published studies evaluating the impact of succinylcholine on reproduction and development to support Sections 8 and 13 of

the label in accordance with the Pregnancy, Lactation, and Labeling Rule (PLLR). Based on this information, the Applicant proposed to add language reflecting published nonclinical data that demonstrated (b) (4) (b) (4) (b) (4). Although the pharmacology/toxicology review team agrees that some of these studies were well-conducted, based on the long history of clinical use of succinylcholine in pregnant patients, these data do not appear to add new information to the safety profile of the drug, and was, therefore, not included in the final drug product labeling.

The Division concurs with the conclusions of the pharmacology/toxicology review team that there are no outstanding nonclinical issues that would prevent approval.

5. Clinical Pharmacology

The Applicant did not conduct any clinical pharmacology or biopharmaceutics studies, and no clinical pharmacology published literature was submitted in support of this application. As previously discussed, a biowaiver was submitted and reviewed by the biopharmaceutics team. Refer to Section 3 of this review for additional information regarding the biopharmaceutics review.

The clinical pharmacology review team did not identify any issues that would prevent approval, and the Division concurs.

6. Clinical Microbiology

Succinylcholine Chloride is not a therapeutic antimicrobial agent, therefore, clinical microbiology data were neither required nor submitted.

7. Clinical/Statistical- Efficacy

The Applicant did not conduct any clinical studies in support of the efficacy of their drug product, and is relying on the Agency's previous finding of efficacy for NDA 008845, Quelicin. Therefore, because no new indications are being sought, and the submitted waiver for the requirement for in vivo bioavailability/bioequivalency studies is acceptable, there are no efficacy issues identified that would preclude approval of this application.

In response to an Information Request sent during the filing review, the Applicant submitted the requested Integrated Summary of Efficacy (ISE), which included summaries of information from meta-analyses and systematic reviews, randomized controlled studies, prospective studies, retrospective studies, multinational questionnaire surveys, and web-based practitioner surveys. Information in the ISE supported the efficacy of succinylcholine, and specifically that it continues to provide superior intubating conditions compared to rocuronium when administered for rapid sequence intubation, generally performed during emergent conditions or in unstable patients.

During the filing review, clarification was requested as to how this drug presentation (i.e., in a prefilled syringe), could be used to administer a continuous intravenous infusion of succinylcholine, which is recommended in the listed drug prescribing information for long surgical procedures. The Applicant stated that their drug product can be administered as a continuous intravenous infusion by mixing the required amount of succinylcholine into an infusion bag containing either 5% dextrose or 0.9% sodium chloride for a resulting concentration of 1 to 2 mg/mL succinylcholine. There were initial concerns about the number of syringes needed for long surgical procedures, and whether injection of multiple syringes into an infusion bag increases the risk of medication error. Specifically, based on information in the published literature[2], continuous infusions lasting approximately one to three hours would require administration of 3 to 11 syringes (diluted). The Applicant argued that because the 1000 mg/10 mL presentation of Quelicin is no longer marketed, infusion solutions must be made from either several succinylcholine vials or prefilled syringes, and that the risk of medication error is likely no greater if the drug is coming from a prefilled syringe, versus a vial. The Division agrees with this rationale, and further notes that continuous succinylcholine infusions are not commonly used in clinical practice, based in part on the development of intermediate-acting non-depolarizing muscle relaxants, such as rocuronium, and effective reversal agents, such as sugammadex.

The Division has no efficacy concerns regarding this drug product that would preclude approval.

8. Safety

The Applicant did not conduct any clinical studies in support of the safety of succinylcholine chloride, and is relying on the Agency's previous finding of safety for NDA 008845, Quelicin, and information in the published literature.

In response to an Information Request sent during the filing review, the Applicant submitted the requested benefit:risk analysis and the Integrated Summary of Safety (ISS), which included the following information:

- An analysis and discussion of major safety results, including non-fatal serious adverse events and adverse events of special interest
- A FAERS search from the most recently approved Quelicin™ label (at the time of NDA filing) to the time of NDA submission
- A review of the worldwide published literature to identify new potential safety concerns that have not been incorporated into the most recently approved labeling of Quelicin.

[2] Ramsey FM, Lebowitz PW, Savarese JJ, Ali HH. Clinical characteristics of long term succinylcholine neuromuscular blockade during balance anesthesia. *Anesth Analg* 1980; 59: 110-116. Brandom BW, Woelfel SK, Cook DR, Weber S, Powers DM, Weakly IN. Comparison of mivacurium and suxamethonium administered by bolus and infusion. *Br J Anaesth* 1989; 62: 488-493. Chen YA, Fan SZ, Lee PC, Shi JJ, Tsai YC, Chang CL, et al. Continuous Succinylcholine Infusion and Phase II Block in Short Surgical Procedures. Ma Zui Xue Za Zhi (*Anaesthesiologica Sinica*). 1993; 31:253-256.

The Applicant summarized the safety findings by adverse drug reactions, based on clinical study and postmarket experience; contraindications; special warnings and precautions; and safety in special populations. The Applicant's review of available safety information did not identify any new safety signals associated with the administration of succinylcholine in a clinical setting. There were reports of unlabeled adverse reactions, including increased creatine kinase (CK), sore throat, and bronchospasm; however, those are likely the result of known adverse reactions described in labeling (i.e., elevated CK in the setting of rhabdomyolysis, bronchospasm described as bronchoconstriction), or unrelated to the administration of succinylcholine (i.e., sore throat).

The risks of administration of succinylcholine are well-described in the published literature and in the listed drug labeling. Specific safety concerns related to the pediatric age group include acute rhabdomyolysis, hyperkalemia, ventricular dysrhythmias, cardiac arrest, and death in patients with underlying neuromuscular disorders, such as Duchenne's muscular dystrophy. Clinically relevant hyperkalemia can occur independent of an undiagnosed myopathy, and particularly when other potassium-sparring medications are co-administered, and in circumstances of major burns, multiple trauma, extensive denervation of skeletal muscle, or upper motor neuron injury. Exposure to succinylcholine is also known to trigger malignant hyperthermia, an inherited life-threatening condition due to sustained skeletal muscle contraction resembling a hypermetabolic state.

The Applicant submitted one published study[3] in the 120-day safety update. The objective of the randomized study was to determine whether pretreatment with intravenous magnesium sulfate ($MgSO_4$) followed by a standard intubating dose of rocuronium achieved superior intubating conditions compared with succinylcholine. The primary endpoint was the rate of excellent intubating conditions 60 seconds after administration of the neuromuscular blocking agent. Secondary endpoints were vital sign measurements before induction, before and after intubation, and adverse events up to 24 hours postoperatively. The results indicated that pretreatment with intravenous $MgSO_4$ followed by rocuronium did not provide superior intubating conditions compared to succinylcholine. The incidence of adverse events, however, including those related to muscle pain and histamine release, was higher in the succinylcholine treatment group. Because myalgias and histamine release are known adverse reactions associated with administration of succinylcholine, the results from this study do not adversely impact the assessment of the safety profile of this drug product.

There do not appear to be any specific safety concerns related to the clinical use of this prefilled syringe presentation that would preclude approval. The syringe is not novel and does not require specialized training that would increase the hazards of use under circumstances of inadequate training. This is particularly relevant for life-saving medications, of which succinylcholine is considered. The Applicant argues that the risk of neuromuscular blocking medication errors will decrease with use of this prefilled syringe presentation based on the lack of practitioner withdrawal from a vial and syringe labeling. This may be true; however, it is

[3] Czarnetzki, C et al. Rapid sequence induction with a standard intubation dose of rocuronium after magnesium pretreatment compared with succinylcholine: a randomized clinical trial. *Anes Anal*. 2020.

worth noting that syringe mix-ups and medication errors can occur whether the syringe is labeled by the individual practitioner or the manufacturer.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

Safety and effectiveness of succinylcholine chloride have been established in pediatric patient age groups, neonate to adolescent. Because this formulation does not represent a new route of administration, new indication, new dosage form, or new dosing regimen, and does not contain new active ingredients, pediatric studies under the Pediatric Research Equity Act (PREA) are not required.

11. Other Relevant Regulatory Issues

The Applicant did not conduct any clinical studies, therefore has not submitted, nor was it required, a financial disclosure statement.

During the review cycle, there was discussion whether this application should have been submitted as an abbreviated new drug application (ANDA) because it is a duplicate of the 100 mg/5 mL (20 mg/mL) presentation of Hospira's NDA 008845 Quelicin (succinylcholine chloride) injection. For information regarding the decision to approve this application via the 505(b)(2) regulatory pathway, refer to the Deviation Memorandum dated August 10, 2021.

12. Labeling

The listed drug label was not in PLR or PLLR format at the time of NDA filing; therefore, the Applicant rearranged information in the Quelicin label based on the guidance documents for each labeling rule, and edited where necessary to reflect single patient use, single dose prefilled syringe. The Applicant did not request additional indications or propose different dosing regimens. During the review cycle, the Quelicin label was converted to PLR format and the Applicant's draft drug label was harmonized accordingly.

The Applicant provided a reasonable rationale for the use of the prefilled syringe during continuous intravenous infusion. Because this is rarely done in clinical practice, and the manner in which it is done is similar enough to the listed drug infusion preparation, the Division has no additional concerns regarding this proposed dosing regimen.

All box warnings and other safety information are the same for the listed drug and the proposed drug.

The review team in the Division of Pediatrics and Maternal Health (DPMH) was consulted during the review cycle and specifically asked to comment on the acceptability of the Applicant's PLLR format of the draft label. The team concluded that the literature and data reviewed did not identify any new safety concerns since the previous DPMH review for succinylcholine exposure in pregnancy, lactation, and females and males of reproductive potential. DPMH recommends minor edits to subsections 8.1 and 8.2 based on previous DPMH edits to the Quelicin label.

Carton and Container Labeling
The review team in Division of Medication Error Prevention and Analysis (DMEPA) concluded that while the Applicant did not implement all of the carton and container labeling recommendations, the rationale provided was deemed acceptable. Specifically, the Applicant stated they were unable to include 'usual dosage' on the container label due to space constraints. The Applicant further stated that currently marketed prefilled syringes do not include this statement in their container label. Additionally, the Applicant stated that embossing 'paralyzing agent' on the luer lock syringe cap is not possible, but did agree to include the statement at two separate locations and orientations on the syringe label.

The DMEPA review team believes the Applicant took reasonable steps to mitigate medication errors, and had no additional concerns regarding the carton and container labeling. Refer to the reviews completed by Dr. Sofanit Getahun for additional information.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval.

Benefit:Risk Assessment
The benefits of succinylcholine 100 mg/5 mL prefilled syringes outweigh the potential risks and the application is approved.

Postmarketing Requirments
There are no postmarketing requirements or commitments for this application. As noted in Section 10, PREA is not triggered and pediatric studies are not required.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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