Press Release

Hikma launches first prefilled syringe of Succinylcholine Chloride Injection, USP

London, 24 October 2022 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Succinylcholine Chloride Injection, USP, in prefilled syringe (PFS) form. The 100mg/5mL PFS has been launched in the US and is the first FDA approved PFS for this product to be introduced in the market. Succinylcholine Chloride is an important medicine used in hospitals for general anesthesia, to facilitate tracheal intubation, and to provide muscle relaxation during surgery or mechanical ventilation.

Riad Mishlawi, President of Injectables said, "We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that will help improve patient care. That is why I am very pleased to launch the first prefilled syringe form of Succinylcholine Chloride, which can help to treat patients faster and more easily. As one of the largest manufacturers of generic injectable medicines, we are committed to expanding our portfolio and making affordable medicines accessible to those in need."

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 130 products.

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across the United States (US), the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 8,700 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm,

[1] Source: IQVIA MAT through August 2022, generic injectable volumes by eaches, excluding branded generics.

hikma.

are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

Important Safety Information for Succinylcholine Chloride Injection, USP, 100mg/5mL:

BOXED WARNING

WARNING: VENTRICULAR DYSRHYTHMIAS, CARDIAC ARREST, AND DEATH FROM HYPERKALEMIC RHABDOMYOLYSIS IN PEDIATRIC PATIENTS

- **Acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death has occurred after the administration of succinylcholine to apparently healthy pediatric patients who were subsequently found to have undiagnosed skeletal muscle myopathy, most frequently Duchenne muscular dystrophy *[see Warnings and Precautions (5.1)]*.**
- **When a healthy appearing pediatric patient develops cardiac arrest within minutes after administration of Succinylcholine Chloride Injection, not felt to be due to inadequate ventilation, oxygenation or anesthetic overdose, immediate treatment for hyperkalemia should be instituted. In the presence of signs of malignant hyperthermia, appropriate treatment should be instituted concurrently *[see Warnings and Precautions (5.1)]*.**
- **Reserve the use of Succinylcholine Chloride Injection in pediatric patients for emergency intubation or instances where immediate securing of the airway is necessary, e.g., laryngospasm, difficult airway, full stomach, or for intramuscular use when a suitable vein is inaccessible *[see Warnings and Precautions (5.1)]*.**

CONTRAINDICATIONS

Succinylcholine Chloride Injection is contraindicated:

- in patients with skeletal muscle myopathies *[see Warnings and Precautions (5.1)]*
- in patients with known hypersensitivity to succinylcholine. Severe anaphylactic reactions to succinylcholine have been reported *[see Warnings and Precautions (5.2)]*
- after the acute phase of injury following major burns, multiple trauma, extensive denervation of skeletal muscle, or upper motor neuron injury, which may result in severe hyperkalemia and cardiac arrest *[see Warnings and Precautions (5.4)]*
- in patients with personal or familial history of malignant hyperthermia *[see Warnings and Precautions (5.5)]*

WARNINGS & PRECAUTIONS

- **Ventricular Dysrhythmias, Cardiac Arrest, and Death From Hyperkalemic Rhabdomyolysis in Pediatric Patients:** There have been reports of ventricular dysrhythmias, cardiac arrest, and death secondary to acute rhabdomyolysis with hyperkalemia in apparently healthy pediatric patients who received succinylcholine. Many of these pediatric patients were subsequently found to have a skeletal muscle myopathy such as Duchenne muscular dystrophy whose clinical signs were not obvious.
- **Anaphylaxis:** Severe anaphylactic reactions to neuromuscular blocking agents, including succinylcholine, have been reported. These reactions have, in some cases, been life-threatening and fatal.
- **Risk of Death Due to Medication Errors:** Administration of Succinylcholine Chloride Injection results in paralysis, which may lead to respiratory arrest and death; this progression may be more likely to occur in a patient for whom it is not intended.
- **Hyperkalemia:** Succinylcholine Chloride Injection may induce serious cardiac arrhythmias or cardiac arrest due to hyperkalemia in patients with electrolyte abnormalities and those who may have digitalis toxicity.
- **Malignant Hyperthermia:** Succinylcholine administration has been associated with acute onset of malignant hyperthermia, a potentially fatal hypermetabolic state of skeletal muscle. The risk of developing malignant hyperthermia following succinylcholine administration increases with the concomitant administration of volatile anesthetics.
- **Bradycardia:** Intravenous bolus administration of Succinylcholine Chloride Injection in pediatric patients (including infants) may result in profound bradycardia or, rarely, asystole. In both adult and pediatric patients the incidence of bradycardia, which may progress to asystole, is higher following a second dose of succinylcholine. The incidence and severity of bradycardia is higher in pediatric patients than adults.
- **Increase in Intraocular Pressure:** Succinylcholine causes an increase in intraocular pressure. Avoid

Succinylcholine Chloride Injection in instances in which an increase in intraocular pressure is undesirable (e.g., narrow angle glaucoma, penetrating eye injury) unless the potential benefit of its use outweighs the potential risk.

- **Prolonged Neuromuscular Block due to Phase II Block and Tachyphylaxis:** When Succinylcholine Chloride Injection is given over a prolonged period of time, the characteristic depolarization block of the myoneural junction (Phase I block) may change to a block with characteristics superficially resembling a nondepolarizing block (Phase II block). Prolonged respiratory muscle paralysis or weakness may be observed in patients manifesting this transition to Phase II block. Tachyphylaxis occurs with repeated administration.
- **Risk of Prolonged Neuromuscular Block in Patients with Reduced Plasma Cholinesterase Activity:** Succinylcholine Chloride Injection is not recommended in patients with known reduced plasma cholinesterase (pseudocholinesterase) activity due to the likelihood of prolonged neuromuscular block following administration of Succinylcholine Chloride Injection in such patients.
- **Risk of Additional Trauma in Patients with Fractures or Muscle Spasms:** Succinylcholine Chloride Injection should be employed with caution in patients with fractures or muscle spasm because the initial muscle fasciculations may cause additional trauma.
- **Increase in Intracranial Pressure:** Succinylcholine Chloride Injection may cause a transient increase in intracranial pressure; however, adequate anesthetic induction prior to administration of Succinylcholine Chloride Injection will minimize this effect.
- **Risk of Aspiration due to Increase in Intragastric Pressure:** Succinylcholine may increase intragastric pressure, which could result in regurgitation and possible aspiration of stomach contents.
- **Prolonged Neuromuscular Block in Patients with Hypokalemia or Hypocalcemia:** Neuromuscular blockade may be prolonged in patients with hypokalemia (e.g., after severe vomiting, diarrhea, digitalisation and diuretic therapy) or hypocalcemia (e.g., after massive transfusions).
- **Risks due to Inadequate Anesthesia:** Neuromuscular blockade in the conscious patient can lead to distress. Use Succinylcholine Chloride Injection in the presence of appropriate sedation or general anesthesia.

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Ventricular Dysrhythmias, Cardiac Arrest, and Death from Hyperkalemic Rhabdomyolysis in Pediatric Patients *[see Warnings and Precautions (5.1)]*
- Anaphylaxis *[see Warnings and Precautions (5.2)]*
- Hyperkalemia *[see Warnings and Precautions (5.4)]*
- Malignant Hyperthermia *[see Warnings and Precautions (5.5)]*
- Bradycardia *[see Warnings and Precautions (5.6)]*
- Increase in Intraocular Pressure *[see Warnings and Precautions (5.7)]*
- Prolonged Neuromuscular Block due to Phase II Block and Tachyphylaxis *[see Warnings and Precautions (5.8)]*

The following adverse reactions associated with the use of succinylcholine were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular disorders: Cardiac arrest, arrhythmias, bradycardia, tachycardia, hypertension, hypotension
Electrolyte disorders: Hyperkalemia
Eye disorders: Increased intraocular pressure
Gastrointestinal disorders: Excessive salivation
Immune system disorders: Hypersensitivity reactions including anaphylaxis (in some cases life threatening and fatal)
Musculoskeletal disorders: Malignant hyperthermia, rhabdomyolysis with possible myoglobinuric acute renal failure, muscle fasciculation, jaw rigidity, postoperative muscle pain
Respiratory disorders: Prolonged respiratory depression or apnea
Skin disorders: Rash

DRUG INTERACTIONS

Drugs that May Affect the Neuromuscular Blocking Action of Succinylcholine Chloride Injection
Drugs that may enhance the neuromuscular blocking action of succinylcholine include: promazine, oxytocin, aprotinin, certain non-penicillin antibiotics, quinidine, β-adrenergic blockers, procainamide, lidocaine, trimethaphan, lithium carbonate, magnesium salts, quinine, chloroquine, isoflurane, desflurane, metoclopramide, and terbutaline.

The neuromuscular blocking effect of succinylcholine may be enhanced by drugs that reduce plasma cholinesterase activity (e.g., chronically administered oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors) or by drugs that irreversibly inhibit plasma cholinesterase *[see Warnings and Precautions (5.9)].*

If other neuromuscular blocking agents are to be used during the same procedure, consider the possibility of a synergistic or antagonistic effect.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Available data from published literature from case reports and case series over several decades of use with succinylcholine during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Succinylcholine is used commonly during delivery by caesarean section to provide muscle relaxation. If succinylcholine is used during labor and delivery, there is a risk for prolonged apnea in some pregnant women *(see Clinical Considerations).* Animal reproduction studies have not been conducted with succinylcholine chloride.

Clinical Considerations
Maternal Adverse Reactions
Plasma cholinesterase levels are decreased by approximately 24% during pregnancy and for several days postpartum which can prolong the effect of succinylcholine. Therefore, some pregnant patients may experience prolonged apnea.

Fetal/Neonatal Adverse Reactions
Apnea and flaccidity may occur in the newborn after repeated high doses to, or in the presence of atypical plasma cholinesterase, in the mother.

Labor or Delivery
Succinylcholine is commonly used to provide muscle relaxation during delivery by caesarean section. Succinylcholine is known to cross the placental barrier in an amount that is dependent on the concentration gradient between the maternal and fetal circulation.

Lactation
Risk Summary
There are no data on the presence of succinylcholine or its metabolite in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Succinylcholine Chloride Injection and any potential adverse effects on the breastfed infant from Succinylcholine Chloride Injection or from the underlying maternal condition.

Pediatric Use
Safety and effectiveness of succinylcholine chloride have been established in pediatric patient age groups, neonate to adolescent. Because of a risk of ventricular dysrhythmias, cardiac arrest, and death from hyperkalemic rhabdomyolysis in pediatric patients, reserve the use of Succinylcholine Chloride Injection in pediatric patients for emergency intubation or instances where immediate securing of the airway is necessary, e.g., laryngospasm, difficult airway, full stomach, or for intramuscular use when a suitable vein is inaccessible *[see Warnings and Precautions (5.1)]*.

Intravenous bolus administration of Succinylcholine Chloride Injection in pediatric patients (including infants) may result in profound bradycardia or, rarely, asystole. The incidence and severity of bradycardia is higher in pediatric patients than adults *[see Warnings and Precautions (5.6)]*.

The effective dose of Succinylcholine Chloride Injection in pediatric patients may be higher than that predicted by body weight dosing alone *[see Dosage and Administration (2.3)]*.

Geriatric Use
Clinical studies of succinylcholine chloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Information
- Succinylcholine Chloride Injection is for intravenous or intramuscular use only.
- Succinylcholine Chloride Injection must be administered under supervision of experienced clinicians who are familiar with its actions and with appropriate neuromuscular monitoring techniques.
- Succinylcholine Chloride Injection should be administered only by those skilled in the management of artificial respiration and only when facilities are instantly available for tracheal intubation and for providing adequate ventilation of the patient, including the administration of oxygen under positive pressure and the elimination of CO2. The clinician must be prepared to assist or control respiration.
- The dosage of Succinylcholine Chloride Injection should be individualized and should always be determined by the clinician after careful assessment of the patient.
- To avoid distress to the patient, do not administer Succinylcholine Chloride Injection before unconsciousness has been induced *[see Warnings and Precautions (5.14)].*
- The occurrence of bradyarrhythmias with administration of Succinylcholine Chloride Injection may be reduced by pretreatment with anticholinergics (e.g., atropine) *[see Warnings and Precautions (5.6)].*
- Monitor neuromuscular function with a peripheral nerve stimulator when using Succinylcholine Chloride Injection by infusion *[see Dosage and Administration (2.2), Warnings and Precautions (5.8)].*
- Visually inspect Succinylcholine Chloride Injection for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer solutions that are not clear and colorless.
- Succinylcholine Chloride Injection must be diluted for continuous intravenous infusion *[see Dosage and Administration (2.5)].*

Risk of Medication Errors
Accidental administration of neuromuscular blocking agents may be fatal. Store Succinylcholine Chloride Injection with the prefilled syringe and cap intact, and in a manner that minimizes the possibility of selecting the wrong product *[see Warnings and Precautions (5.3)]*.

Dosage Recommendations for Intravenous Use in Adults
For Short Surgical Procedures
The average dose required to produce neuromuscular blockade and to facilitate tracheal intubation is 0.6 mg/kg Succinylcholine Chloride given intravenously. The optimum intravenous dose of Succinylcholine Chloride Injection will vary among patients and may be from 0.3 mg/kg to 1.1 mg/kg for adults. Following intravenous administration of doses in this range, neuromuscular blockade develops in about 1 minute; maximum blockade may persist for about 2 minutes, after which recovery takes place within 4 to 6 minutes. A 5 to 10 mg test dose of Succinylcholine Chloride Injection may be used to determine the sensitivity of the patient and the individual recovery time *[see Warnings and Precautions (5.9)]*.

For Long Surgical Procedures
Continuous Intravenous Infusion
The dosage of Succinylcholine Chloride Injection administered by continuous intravenous infusion depends upon the duration of the surgical procedure and the need for muscle relaxation.

Diluted solutions containing from 1 mg/mL to 2 mg/mL succinylcholine have commonly been used for continuous intravenous infusion *[see Dosage and Administration (2.5)]*. The more dilute solution (1 mg/mL) is probably preferable from the standpoint of ease of control of the rate of administration of Succinylcholine Chloride Injection

and, hence, of relaxation. Succinylcholine Chloride Injection, 1 mg per mL, may be administered at a rate of 0.5 mg (0.5 mL) per minute to 10 mg (10 mL) per minute to obtain the required amount of relaxation. The amount required per minute will depend upon the individual response as well as the degree of relaxation required. The average rate of continuous intravenous infusion for an adult ranges between 2.5 mg per minute and 4.3 mg per minute.

Monitor neuromuscular function with a peripheral nerve stimulator when using Succinylcholine Chloride Injection by infusion in order to avoid overdose, detect development of Phase II block, follow its rate of recovery, and assess the effects of reversing agents *[see Warnings and Precautions (5.8)].*

Intermittent Intravenous Injection
Intermittent intravenous injections of Succinylcholine Chloride Injection may also be used to provide muscle relaxation for long procedures. An intravenous injection of 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.

Dosage Recommendations for Intravenous Use in Pediatric Patients
For emergency tracheal intubation or in instances where immediate securing of the airway is necessary, the intravenous dose of Succinylcholine Chloride Injection is 2 mg/kg for infants and other small pediatric patients; for older pediatric patients and adolescents the intravenous dose of Succinylcholine Chloride is 1 mg/kg *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].* The effective dose of Succinylcholine Chloride Injection in pediatric patients may be higher than that predicted by body weight dosing alone. For example, the usual adult intravenous dose of 0.6 mg/kg is comparable to a dose of 2 mg/kg to 3 mg/kg in neonates and infants up to 6 months of age and 1 mg/kg to 2 mg/kg in infants up to 2 years of age *[see Clinical Pharmacology (12.3)].*

Dosage Recommendations for Intramuscular Use in Adults and Pediatric Patients
If a suitable vein is inaccessible, Succinylcholine Chloride Injection may be administered intramuscularly at a dose of up to 3 mg/kg to 4 mg/kg to infants, older pediatric patients, or adults. The total dose administered by the intramuscular route should not exceed 150 mg. The onset of effect of succinylcholine given intramuscularly is usually observed in about 2 to 3 minutes.

Preparation of Succinylcholine Chloride Injection
Succinylcholine Chloride Injection is supplied in a single-dose, prefilled syringe, and does not require dilution for intravenous or intramuscular bolus dosing. Succinylcholine Chloride Injection may be diluted for continuous intravenous infusion to 1 mg/mL or 2 mg/mL in a solution such as:

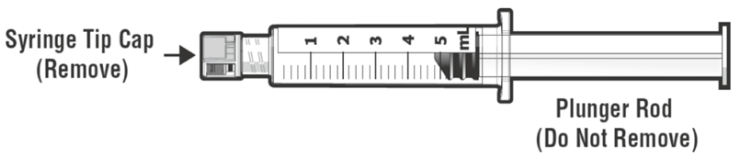
- 5% Dextrose Injection, USP, or
- 0.9% Sodium Chloride Injection, USP

Prepare the diluted Succinylcholine Chloride solution for single patient use only. Store the diluted Succinylcholine Chloride solution in a refrigerator [2°C to 8°C (36°F to 46°F)] and use within 24 hours after preparation. Visually inspect the diluted Succinylcholine Chloride Injection solution for particulate matter and discoloration prior to administration. Do not administer solutions that are not clear and colorless. Discard any unused portion of the diluted Succinylcholine Chloride Injection solution.

Drug Incompatibility
Succinylcholine Chloride Injection is acidic (pH 3.5) and may not be compatible with alkaline solutions having a pH greater than 8.5 (e.g., barbiturate solutions). Therefore, do not mix Succinylcholine Chloride Injection with alkaline solutions.

Instructions for Use of Prefilled Syringe
CAUTION: Assure that the needle or Needleless Luer Access Device (NLAD) is securely attached before beginning the injection. Visually inspect the syringe needle or syringe-NLAD connection before and during drug administration.

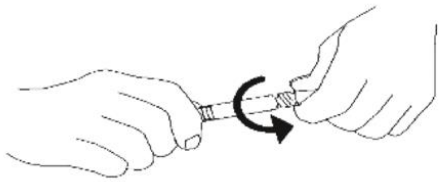
<u>Administration Technique</u>
Figure 1



Succinylcholine Chloride Injection may be administered intravenously or intramuscularly.
1. Inspect the outer packaging (plastic overwrap) and the syringe label by verifying:
   - plastic overwrap integrity
   - drug name
   - drug strength
   - fill volume
   - route of administration
   - expiration date to be sure that the drug has not expired
   - sterile field applicability

Do not use if package has been damaged
2. Open the outer packaging and remove the syringe from the plastic overwrap. Do not pop syringe through.
3. Perform visual inspection on the syringe by verifying:
   - absence of syringe damage
   - absence of external particles
   - absence of internal particles
   - proper drug color
4. Push plunger rod slightly while tip cap is still on to break the stopper loose.
5. Remove tip cap by twisting it off. (See Figure 2)

Figure 2



6. Discard the tip cap.
7. Expel air bubble.
8. Connect the syringe to an appropriate injection connection depending on the route of administration. Before injection, ensure that the syringe is securely attached to the needle or NLAD.
9. Depress plunger rod to deliver the required dose of medication. Ensure that pressure is maintained on the plunger rod during the entire administration. Waste residual medication per institutional policy.
10. Remove syringe from NLAD (if applicable) and discard into appropriate receptacle. When a needle is connected to the syringe, to prevent needlestick injuries, do not recap needles.

NOTES**:**
- All steps must be performed sequentially
- Do not autoclave syringe
- Do not use this product on a sterile field
- Do not introduce any other fluid into the syringe at any time
- This product is for single dose only; discard unused portion

OVERDOSAGE

Overdosage with Succinylcholine Chloride Injection may result in neuromuscular block beyond the time needed for surgery and anesthesia. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. The primary treatment is maintenance of a patent airway and respiratory support until recovery of normal respiration is assured. Depending on the dose and duration of Succinylcholine Chloride Injection administration, the characteristic depolarizing neuromuscular block (Phase I) may change to a block with characteristics superficially resembling a non-depolarizing block (Phase II) *[see Warnings and Precautions (5.8)]*.

INDICATIONS AND USAGE

Succinylcholine Chloride Injection is 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

HOW SUPPLIED/STORAGE AND HANDLING

NDC No.	Container	Size (mL)	mg/mL	mg (total)	mOsmol/mL (calc.)
0641-6234-10	Prefilled single-dose Syringe	5	20	100	0.338

Succinylcholine Chloride Injection, USP is supplied as a clear, colorless solution in the following concentration and package:

NDC 0641-6234-10, 5 mL single-dose prefilled syringes packaged in a carton of 10.

Refrigeration of the undiluted Succinylcholine Chloride Injection will assure full potency until expiration date. All units carry a date of expiration.

Store in refrigerator 2°C to 8°C (36°C to 46°F). The single-dose syringes are stable for up to 14 days at room temperature without significant loss of potency.

Discard unused portion.

ENDING INFORMATION

For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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