hikma.

Press Release

Hikma launches Fentanyl Citrate Injection, USP, in a prefilled syringe in the US

London, 20 February 2024 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Fentanyl Citrate Injection, USP, in 25mcg/0.5mL and 50mcg/mL doses. The product has been launched in the US and is indicated for:

- analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
- use as a narcotic analgesic supplement in general or regional anesthesia.
- administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
- use as an anesthetic agent with oxygen in selected high-risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

Hikma is introducing the first FDA approved 25mcg/0.5mL presentation to the US market and we are pleased to expand our portfolio with this launch, broadening the choice of medicines available to hospitals.

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 150 products. We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care.

- ENDS –

This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

Enquiries

Hikma Pharmaceuticals PLC

Susan Ringdal
EVP, Strategic Planning and Global Affairs

+44 (0)20 7399 2760/ +44 7776 477050
uk-investors@hikma.uk.com

Steve Weiss
David Belian
US Communications and Public Affairs

+1 732 720 2830/ +1 732 788 8279
+1 732 720 2814/+1 848 254 4875
uscommunications@hikma.com

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

[1] Source: IQVIA MAT December 2023, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

hikma.

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 North America, 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 8,800 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, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

Important Safety Information for Fentanyl Citrate Injection, USP, 25mcg/0.5mL and 50mcg/mL:

Please see package insert for referenced section numbering, where appropriate.

BOXED WARNING

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF FENTANYL CITRATE INJECTION

Addiction, Abuse, and Misuse
Because the use of Fentanyl Citrate Injection exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.1)*].

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Fentanyl Citrate Injection, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of Fentanyl Citrate Injection are essential [see *Warnings and Precautions (5.2)].*

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of Fentanyl Citrate Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate [see *Warnings and Precautions (5.4)*, *Drug Interactions (7)*].

Cytochrome P450 3A4 Interaction
The concomitant use of Fentanyl Citrate Injection with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving Fentanyl Citrate Injection and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions (5.3)*, *Drug Interactions (7)*, *Clinical Pharmacology (12.3)*].

CONTRAINDICATIONS

Fentanyl Citrate Injection is contraindicated in patients with:
- Hypersensitivity to fentanyl (e.g., anaphylaxis) *[See Adverse Reactions (6)]*

WARNINGS & PRECAUTIONS

- **Addiction, Abuse, and Misuse –** Fentanyl Citrate Injection contains fentanyl, a Schedule II controlled substance. As an opioid, Fentanyl Citrate Injection exposes users to the risks of addiction, abuse, and misuse.
- **Life-Threatening Respiratory Depression –** Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death.
- **Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants –** When benzodiazepines or other CNS depressants are used with Fentanyl Citrate Injection, pulmonary arterial pressure may be

decreased. When high dose or anesthetic dosages of Fentanyl Citrate Injection are employed, even relatively small dosages of diazepam may cause cardiovascular depression. When Fentanyl Citrate Injection is used with CNS depressants, hypotension can occur. Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Fentanyl Citrate Injection with benzodiazepines or other CNS depressants, including alcohol (e.g., nonbenzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids).

- **Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers –** Concomitant use of Fentanyl Citrate Injection with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may exacerbate respiratory depression.
- **Risks of Muscle Rigidity and Skeletal Muscle Movement –** Fentanyl Citrate Injection may cause muscle rigidity, particularly involving the muscles of respiration. Skeletal muscle rigidity also has been reported to occur or recur infrequently in the extended postoperative period usually following high dose administration. In addition, skeletal muscle movements of various groups in the extremities, neck, and external eye have been reported during induction of anesthesia with Fentanyl Citrate Injection.
- **Severe Cardiovascular Depression –** Fentanyl Citrate Injection may cause severe bradycardia, severe hypotension including orthostatic hypotension, and syncope.
- **Opioid-Induced Hyperalgesia and Allodynia** – Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics.
- **Serotonin Syndrome with Concomitant Use of Serotonergic Drugs –** Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazadone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). This may occur within the recommended dosage range.
- **Adrenal Insufficiency –** Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- **Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, or Head Injury –** In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Fentanyl Citrate Injection may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure.
- **Risks of Use in Patients with Gastrointestinal Conditions –** Fentanyl may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase.
- **Increased Risks of Seizures in Patients with Seizure Disorders –** Fentanyl may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical setting associated with seizures.
- **Risk of Driving and Operating Machinery –** Fentanyl Citrate Injection may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery after Fentanyl Citrate Injection administration.
- **Risks due to Interaction with Neuroleptic Agents –** Many neuroleptic agents have been associated with QT prolongation, Torsades de Pointes, and cardiac arrest. Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of Fentanyl Citrate Injection combined with a neuroleptic.

ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Severe Cardiovascular Depression *[see Warnings and Precautions (5.6)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.7)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*

The following adverse reactions associated with the use of fentanyl 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.

As with other opioid agonists, the most common serious adverse reactions reported to occur with fentanyl are respiratory depression, apnea, rigidity and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, diaphoresis, serotonin syndrome, adrenal insufficiency, and anaphylaxis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. When a tranquilizer is used with Fentanyl Citrate Injection, the following adverse reactions can occur: chills and/or shivering, restlessness and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-Parkinson agents. Postoperative drowsiness is also frequently reported following the use of neuroleptics with fentanyl citrate.

Cases of cardiac dysrhythmias, cardiac arrest, and death have been reported following the use of fentanyl citrate with a neuroleptic agent.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Fentanyl Citrate Injection.
Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time [see *Clinical Pharmacology (12.2)*].
Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration [*see Warnings and Precautions (5.7)*].
Hypoglycemia: Causes of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

DRUG INTERACTIONS

Inhibitors of CYP3A4
The concomitant use of Fentanyl Citrate Injection and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of Fentanyl Citrate Injection is achieved.

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.

CYP3A4 Inducers
The concomitant use of Fentanyl Citrate Injection and CYP3A4 inducers can decrease the plasma concentration of fentanyl, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl.

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

Benzodiazepines and Other Central Nervous System (CNS) Depressants
The concomitant use of Fentanyl Citrate Injection with CNS depressants may result in decreased pulmonary artery pressure and may cause hypotension. Even small dosages of diazepam may cause cardiovascular depression when added to high dose or anesthetic dosages of Fentanyl Citrate Injection. As postoperative analgesia, concomitant use of Fentanyl Citrate Injection can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

Monoamine Oxidase Inhibitors
MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics
May reduce the analgesic effect of Fentanyl Citrate Injection and/or precipitate withdrawal symptoms.

Muscle Relaxants
Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Diuretics
Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Anticholinergic Drugs
The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Neuroleptics
Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of Fentanyl Citrate Injection combined with a neuroleptic.

Nitrous oxide
Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of Fentanyl Citrate Injection.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with Fentanyl Citrate Injection in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. No evidence of malformations was noted in animal studies completed to date.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Labor or Delivery
There are insufficient data to support the use of fentanyl in labor or delivery. Therefore, such use is not recommended. Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Fentanyl Citrate Injection is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including Fentanyl Citrate Injection, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Lactation
Risk Summary
Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.38%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fentanyl Citrate Injection and any potential adverse effects on the breastfed infant from Fentanyl Citrate Injection or from the underlying maternal condition.

Clinical Considerations
Monitor infants exposed to fentanyl through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Females and Males of Reproductive Potential
Infertility
Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Pediatric Use
The safety and efficacy of Fentanyl Citrate Injection in pediatric patients under two years of age has not been established.

Rare cases of unexplained clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included combined use of fentanyl, pancuronium and atropine. A direct cause and effect relationship between the combined use of these drugs and the reported cases of methemoglobinemia has not been established.

Geriatric Use
Elderly patients (aged 65 years or older) may have increased sensitivity to fentanyl. In general, use caution when selecting a dosage for an elderly patient, 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.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Fentanyl Citrate Injection slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression.

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hepatic Impairment
Fentanyl Citrate Injection should be administered with caution to patients with liver dysfunction because of the extensive hepatic metabolism. Reduce the dosage as needed and monitor closely for signs of respiratory depression, sedation, and hypotension.

Renal Impairment
Fentanyl Citrate Injection should be administered with caution to patients with kidney dysfunction because of the renal excretion of Fentanyl Citrate Injection and its metabolites. Reduce the dosage as needed and monitor closely for signs of respiratory depression, sedation, and hypotension.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions
Fentanyl Citrate Injection should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

- Ensure that an opioid antagonist, resuscitative and intubation equipment, and oxygen are readily available.
- Individualize dosage based on factors such as age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.
- Monitor vital signs routinely.

As with other potent opioids, the respiratory depressant effect of fentanyl may persist longer than the measured analgesic effect. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia.

If Fentanyl Citrate Injection is administered with a CNS depressant, become familiar with the properties of each drug, particularly each product's duration of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available *[see Warnings and Precautions (5.4)]*. Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Dosage

Premedication in Adults

50 mcg to 100 mcg may be administered intramuscularly 30 to 60 minutes prior to surgery.

Adjunct to General Anesthesia

See Dosage Range Charts in Table 1 of package insert.

Adjunct to Regional Anesthesia

50 mcg to 100 mcg may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

Postoperatively (recovery room)

50 mcg to 100 mcg may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

For Induction and Maintenance in Children 2 to 12 Years of Age

A reduced dose as low as 2 mcg/kg to 3 mcg/kg is recommended.

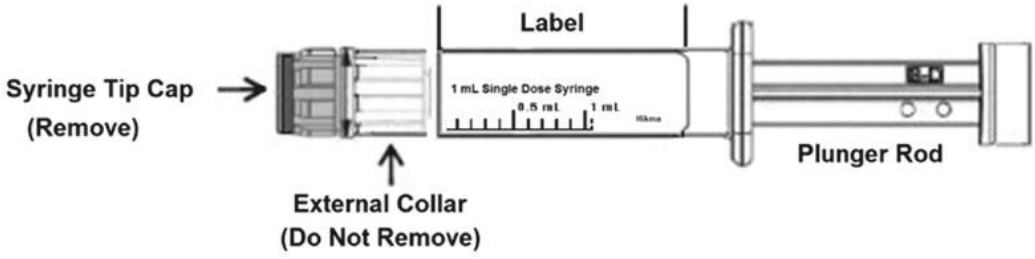
As a General Anesthetic

As a technique to attenuate the responses to surgical stress without the use of additional anesthetic agents, doses of 50 mcg/kg to 100 mcg/kg may be administered with oxygen and a muscle relaxant. In certain cases, doses up to 150 mcg/kg may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

Instructions for Use of Fentanyl Citrate Injection Prefilled Syringe

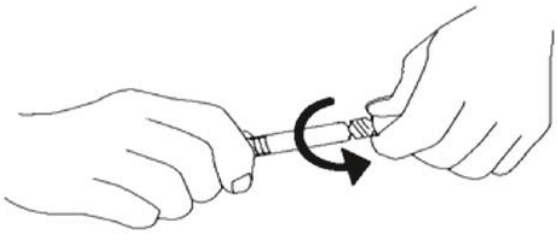
CAUTION: Glass syringes may malfunction, break or clog when connected to some Needleless Luer Access Devices (NLADs) and needles. The external collar must remain attached to the syringe *(See Figure 1)*. Spontaneous disconnection of this glass syringe from needles and NLADs with leakage of drug product may occur. Assure that the needle or NLAD is securely attached before beginning the injection. Inspect the glass syringe-needle or glass syringe –NLAD connection before and during drug administration.

Figure 1



1. Inspect the integrity of the plastic tube, cap and tamper evident seal. Do not use if the tamper evident seal has been damaged.
2. Break the tamper evident seal when removing the cap to access the syringe.
3. Push plunger rod slightly to break the stopper loose while tip cap is still on.
4. Remove tip cap by twisting it off. (See Figure 2)

Figure 2



5. Connect the syringe to an appropriate injection connection.
6. Depress plunger rod to deliver the required dose.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
Fentanyl Citrate Injection contains fentanyl, a Schedule II controlled drug substance.

Abuse
Fentanyl Citrate Injection contains fentanyl, a substance with a high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by healthcare provider or for whom it was not prescribed. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of Fentanyl Citrate Injection increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of Fentanyl Citrate Injection with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of Fentanyl Citrate Injection abuse include those with a history of prolonged use of any opioid, including products containing fentanyl, those with a history of drug or alcohol abuse, or those who use Fentanyl Citrate Injection in combination with other abused drugs.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare providers(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Fentanyl Citrate Injection, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures to limit abuse of opioid drugs.

<u>Risks Specific to Abuse of Fentanyl Citrate Injection</u>
Abuse of Fentanyl Citrate Injection poses a risk of overdose and death. The risk is increased with concurrent use of Fentanyl Citrate Injection with alcohol and/or other CNS depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence
Both tolerance and physical dependence can develop during chronic opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Physical dependence is a state that develops as a result of physiological adaptation in a response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dosage reduction of a drug.

Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Fentanyl Citrate Injection should not be abruptly discontinued in a physically-dependent patient. If Fentanyl Citrate Injection is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur, typically characterized by restlessness, lacrimation, rhinorrhea, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs.

OVERDOSAGE

Clinical Presentation
Acute overdose with fentanyl can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose
In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in Fentanyl Citrate Injection, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

INDICATIONS AND USAGE

Fentanyl Citrate Injection is indicated for:
- analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
- use as a narcotic analgesic supplement in general or regional anesthesia.
- administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
- use as an anesthetic agent with oxygen in selected high-risk patients, such as those undergoing open heart

surgery or certain complicated neurological or orthopedic procedures.

HOW SUPPLIED/STORAGE AND HANDLING

Fentanyl Citrate Injection, equivalent to 50 mcg fentanyl base per mL, is a preservative-free solution, supplied as follows:

NDC 0641-6024-10	2 mL *Single Dose* ampuls packaged in 10s
NDC 0641-6247-25	1 mL *Single Dose* vials packaged in 25s
NDC 0641-6027-25	2 mL *Single Dose* vials packaged in 25s
NDC 0641-6025-10	5 mL *Single Dose* ampuls packaged in 10s
NDC 0641-6028-10	5 mL *Single Dose* vials packaged in 10s
NDC 0641-6248-10	1 mL *Single Dose* prefilled syringes in 10s
NDC 0641-6249-10	0.5 mL *Single Dose* prefilled syringes in 10s

For Intravenous Use by Hospital Personnel Specifically Trained in the Use of Narcotic Analgesics:

NDC 0641-6026-05	20 mL *Single Dose* ampuls packaged in 5s
NDC 0641-6029-01	20 mL *Single Dose* vials packaged individually
NDC 0641-6030-01	50 mL *Single Dose* vials packaged individually

PROTECT FROM LIGHT. Keep covered in carton until time of use. Store at 20˚C to 25˚C (68˚F to 77˚F), excursions permitted to 15˚C to 30˚C (59˚F to 86˚F) [See USP Controlled Room Temperature]. Contains no preservative. DISCARD ANY UNUSED CONTENTS.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
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 FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

For Product Inquiry call 1-877-845-0689.

Manufactured by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922 USA

Document Identification Number: HK-2352-v2