hikma.

Press Release

Hikma launches Vecuronium Bromide for Injection

London, April 3, 2020 – Hikma Pharmaceuticals PLC (Hikma, Group), the multinational generic pharmaceutical company, has launched Vecuronium Bromide for Injection, 10mg, in the United States through its US affiliate, Hikma Pharmaceuticals USA Inc.[1]

According to IQVIA, US sales of Vecuronium Bromide for Injection, 10mg, were approximately $6 million in the 12 months ending February 2020.

Vecuronium Bromide for Injection is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Hikma is the third largest US supplier of generic injectable medicines by volume, with a growing portfolio of over 100 products. Today one in every six injectable generic medicines used in US hospitals is a Hikma product.

- ENDS -

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 Ba1/stable Moody's and BB+/positive S&P)

Hikma helps put better health within reach every day for millions of people in more than 50 countries 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 8,600 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] Hikma Pharmaceuticals USA Inc. was formerly known as West-Ward Pharmaceuticals Corp.

hikma.

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

Important Safety Information for Vecuronium Bromide for Injection, 10mg:

BOXED WARNING

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS

Vecuronium bromide is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS & PRECAUTIONS

- **Anaphylaxis:** Severe anaphylactic reactions to neuromuscular blocking agents, including VECURONIUM BROMIDE, have been reported. These reactions have in some cases been life-threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as the immediate availability of appropriate emergency treatment, should be taken. Precautions should also be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents, both depolarizing and non-depolarizing, has been reported in this class of drugs.
- VECURONIUM SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE I.C.U., VECURONIUM OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND WHO ARE FAMILIAR WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR MUSCLE MONITORING TECHNIQUES.
- In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of vecuronium may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.
- **Risk of Death due to Medication Errors:** Administration of vecuronium bromide for 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. Confirm proper selection of intended product and avoid confusion with other injectable solutions that are present in critical care and other clinical settings. If another healthcare provider is administering the product, ensure that the intended dose is clearly labeled and communicated.
- Since allergic cross-reactivity has been reported in this class, request information from your patients about previous anaphylactic reactions to other neuromuscular blocking agents. In addition, inform your patients that severe anaphylactic reactions to neuromuscular blocking agents, including VECURONIUM BROMIDE have been reported.
- Vecuronium is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of

vecuronium should be considered.

- Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to delay in onset time, therefore, dosage should not be increased.
- Experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in vecuronium metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.
- In the intensive care unit, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness, that may be first noted during attempts to wean such patients from the ventilator. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.
- IN THE INTENSIVE CARE UNIT, APPROPRIATE MONITORING, WITH THE USE OF A PERIPHERAL NERVE STIMULATOR TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED TO HELP PRECLUDE POSSIBLE PROLONGATION OF THE BLOCKADE. WHENEVER THE USE OF VECURONIUM OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE I.C.U., IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF VECURONIUM OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T1 OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.
- Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as vecuronium.
- Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not vecuronium is capable of triggering malignant hyperthermia.
- Vecuronium has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

ADVERSE REACTIONS

There have been postmarketing reports of severe allergic reactions (anaphylactic and anaphylactoid reactions) associated with use of neuromuscular blocking agents, including VECURONIUM BROMIDE. These reactions, in some cases, have been life-threatening and fatal. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with vecuronium bromide as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action with vecuronium bromide is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol.

Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit. The administration of vecuronium bromide has been associated with rare instances of hypersensitivity

reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

DRUG INTERACTIONS

Succinylcholine:
Prior administration of succinylcholine may enhance the neuromuscular blocking effect of vecuronium and its duration of action. If succinylcholine is used before vecuronium, the administration of vecuronium should be delayed until the succinylcholine effect shows signs of wearing off.

The use of vecuronium before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Nondepolarizing Neuromuscular Blocking Agents:
Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does vecuronium, therefore, these drugs and vecuronium, may manifest an additive effect when used together. There are insufficient data to support concomitant use of vecuronium and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics:
Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with vecuronium will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of vecuronium may be the same as the balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics:
Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with vecuronium, unexpected prolongation of neuromuscular block should be considered a possibility.

Thiopental:
Reconstituted vecuronium, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions such as thiopental) in the same syringe or administered simultaneously during intravenous infusion through the same needle or through the same intravenous line.

Other:
Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for vecuronium. Vecuronium induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy may enhance the neuromuscular blockade.

USE IN SPECIFIC POPULATIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Teratogenic Effects; Pregnancy Category C:
Animal reproduction studies have not been conducted with vecuronium. It is also not known whether vecuronium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Vecuronium should be given to a pregnant woman only if clearly needed.

Labor and Delivery:
The use of vecuronium in patients undergoing cesarean section has been reported in the literature. Following tracheal intubation with succinylcholine, vecuronium dosages of 0.04 mg/kg (n=11) and 0.06 to 0.08 mg/kg (n=20) were administered. The umbilical venous plasma concentrations were 11% of maternal concentrations at delivery and mean neonate APGAR scores at 5 minutes were ≥ 9 in both reports. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Nursing Mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when vecuronium is administered to a nursing woman.

Pediatric Use:
Infants under 1 year of age but older than 7 weeks also tested under halothane anesthesia, are moderately more sensitive to vecuronium on a mg/kg basis than adults and take about 1.5 times as long to recover. The safety and effectiveness of vecuronium in pediatric patients less than 7 weeks of age have not been established.

Geriatric Use:
Clinical studies of vecuronium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There are some reports in the peer reviewed literature of increased effect and longer duration of action of vecuronium in the elderly compared to younger patients. However, other reports have found no significant differences between healthy elderly and younger adults. Advanced age or other conditions associated with slower circulation time, may be associated with a delay in onset time. Dose selections 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. Close monitoring of neuromuscular function is recommended.

DOSAGE AND ADMINISTRATION

Vecuronium bromide for injection is for intravenous use only.

This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case.

To obtain maximum clinical benefits of vecuronium bromide and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

Infusion of vecuronium bromide should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of vecuronium bromide infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of vecuronium bromide can be prepared by adding vecuronium bromide with an appropriate infusion solution such as Dextrose 5% Injection, Sodium Chloride 0.9% Injection, Dextrose 5% in Sodium Chloride 0.9% Injection, or Lactated Ringer's Injection. Vecuronium bromide is also

compatible in solution with: Sterile Water for Injection and Bacteriostatic Water for Injection (**NOT FOR USE IN NEWBORNS**).

Risk of Medication Errors: Accidental administration of neuromuscular blocking agents may be fatal. Store vecuronium bromide for injection with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product.

Overdosage
The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of vecuronium produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with vecuronium as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants.

Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Pyridostigmine, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of vecuronium. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

The effects of hemodialysis and peritoneal dialysis on plasma levels of vecuronium and its metabolite are unknown.

ENDING INFORMATION

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **http://www.fda.gov/medwatch** or call 1-800-FDA-1088.

Manufactured by:
HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Estrada do Rio da Mó, 8, 8A e 8B – Fervença – 2705-906 Terrugem SNT, Portugal

Distributed by:
Hikma Pharmaceuticals USA Inc. (formerly West-Ward, A Hikma Company)
Eatontown, NJ 07724 USA

Document Identification Number: WW20396