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Press Release

Hikma launches Nicardipine Hydrochloride premixed injection in ready to use bags

London, 4 May 2020 – Hikma Pharmaceuticals PLC (Hikma, Group), the multinational pharmaceutical company, has launched Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection bags in 200mL, the generic version of Cardene®[1], in the United States through its US affiliate, Hikma Pharmaceuticals USA Inc.

Nicardipine Hydrochloride Injection is indicated for the short-term treatment of hypertension when oral therapy is not feasible or desirable. For prolonged control of blood pressure, patients are transferred to oral medication as soon as their clinical condition permits.

According to IQVIA, US sales of Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection, 200mL, were approximately $82 million in the 12 months ending January 2020.

“Nicardipine Hydrochloride Injection is an important medicine used to treat hypertension and Hikma is proud to introduce the first generic Nicardipine in ready to use bags,” said Riad Mishlawi, President of Injectables. “Hikma also markets Nicardipine in 10mL vials and we are pleased to expand our portfolio with this launch, broadening the choice of medicines available to hospitals.”

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.

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About Hikma

(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1/stable Moody's and BB+/positive S&P)

[1] Cardene® is a registered trademark of Baxter International Inc.

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

Important Safety Information for Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection:

CONTRAINDICATIONS

Advanced Aortic Stenosis
Do not use nicardipine in patients with advanced aortic stenosis because of the afterload reduction effect of nicardipine. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

WARNINGS & PRECAUTIONS

- In administrating nicardipine, close monitoring of blood pressure and heart rate is required. Nicardipine may occasionally produce symptomatic hypotension or tachycardia. Avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage.
- No clinical events have been reported suggestive of a too rapid decrease in blood pressure with nicardipine. However, as with any antihypertensive agent, blood pressure lowering should be accomplished over as long a time as is compatible with the patient's clinical status.
- Increases in frequency, duration, or severity of angina have been seen in chronic oral therapy with nicardipine capsules. Induction or exacerbation of angina has been seen in less than 1% of coronary artery disease patients treated with nicardipine. The mechanism of this effect has not been established.
- Nicardipine reduced afterload without impairing myocardial contractility in preliminary hemodynamic studies of CHF patients. However, *in vitro* and in some patients, a negative inotropic effect has been observed. Therefore, monitor vital signs carefully when using nicardipine, particularly in combination with a beta-blocker, in patients with CHF or significant left ventricular dysfunction.
- Since nicardipine is metabolized in the liver, consider lower dosages and closely monitor response. Nicardipine administered intravenously increased hepatic venous pressure gradient by 4 mmHg in cirrhotic patients at high doses (5 mg/20 min) in one study. Use caution in patients with portal hypertension.
- When nicardipine was given to mild-to-moderate hypertensive patients with moderate renal impairment, a significantly lower systemic clearance and higher AUC was observed. These results are consistent with those seen after oral administration of nicardipine. Careful dose titration is advised when treating patients with more than mild renal impairment.
- To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, extravasation, and the rare occurrence of vascular impairment, administer drug through large peripheral veins or central veins rather than arteries or small peripheral veins, such as those on the dorsum of the hand or wrist. To minimize the risk of peripheral venous irritation, consider changing the site of the drug infusion every 12 hours.
- Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta blocker withdrawal. Withdraw beta-blockers gradually.
- Only limited clinical experience exists in use of nicardipine for patients with hypertension from

pheochromocytoma.

ADVERSE REACTIONS

Two hundred forty-four patients participated in two multicenter, double-blind, placebo-controlled trials of nicardipine. Adverse experiences were generally not serious and most were expected consequences of vasodilation. Adverse reactions occasionally required dosage adjustment. Therapy was discontinued in approximately 12% of patients, mainly due to hypotension, headache, and tachycardia. Adverse reactions that occurred more often on nicardipine than on placebo by at least 2% were headache (13%) and nausea/vomiting (4%).

The following adverse reactions have been reported in clinical trials or in the literature during the use of intravenously administered nicardipine: *Body as a Whole* (fever, neck pain), *Cardiovascular* (angina pectoris, atrioventricular block, ST segment depression, inverted T wave, deep-vein thrombophlebitis), *Digestive* (dyspepsia), *Hemic and Lymphatic* (thrombocytopenia), *Metabolic and Nutritional* (hypophosphatemia, peripheral edema), *Nervous* (confusion, hypertonia), *Respiratory* (respiratory disorder), *Special Senses* (conjunctivitis, ear disorder, tinnitus), *Urogenital* (urinary frequency).

DRUG INTERACTIONS

Antihypertensive Agents
Since nicardipine hydrochloride injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and to treat promptly any undesired effects from concomitant administration.

Beta-Blockers
In most patients, nicardipine hydrochloride injection can safely be used concomitantly with beta-blockers. However, monitor response carefully when combining nicardipine hydrochloride injection with a beta blocker in the treatment of congestive heart failure patients.

Cimetidine
Cimetidine has been shown to increase nicardipine plasma concentrations with oral nicardipine administration. Carefully monitor patients receiving the two drugs concomitantly. Data with other histamine-2 antagonists are not available.

Digoxin
Studies have shown that oral nicardipine usually does not alter digoxin plasma concentrations.

Cyclosporine
Concomitant administration of oral or intravenous nicardipine and cyclosporine results in elevated plasma cyclosporine levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Monitor closely plasma concentrations of cyclosporine during nicardipine hydrochloride injection administration, and adjust the dose of cyclosporine accordingly.

Tacrolimus
Concomitant administration of intravenous nicardipine and tacrolimus may result in elevated plasma tacrolimus levels through nicardipine inhibition of hepatic microsomal enzymes, including CYP3A4. Closely monitor plasma concentrations of tacrolimus during nicardipine administration, and adjust the dose of tacrolimus accordingly.

In Vitro Interaction
The plasma protein binding of nicardipine was not altered when therapeutic concentrations of furosemide, propranolol, dipyridamole, warfarin, quinidine, or naproxen were added to human plasma *in vitro*.

USE IN SPECIFIC POPULATIONS

Pregnancy
There are no adequate and well-controlled studies of nicardipine use in pregnant women. There are limited human data in pregnant women with pre-eclampsia and preterm labor. In animal reproduction and developmental toxicity studies, evidence of fetal harm was observed. Therefore use nicardipine during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Nicardipine is minimally excreted into human milk. It is recommended that women who wish to breastfeed should not be given this drug.

Pediatric Use
Safety and efficacy in patients under the age of 18 have not been established.

Geriatric Use
The steady-state pharmacokinetics of nicardipine are similar in elderly hypertensive patients (greater than 65 years) and young healthy adults.

Clinical studies of nicardipine 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 concomitant disease of other drug therapy.

DOSAGE AND ADMINISTRATION

General Information
Individualize dosing based on the severity of hypertension and the response of the patient during dosing. Monitor blood pressure and heart rate both during and after the infusion to avoid tachycardia or too rapid or excessive reduction in either systolic or diastolic blood pressure.

Administer Nicardipine Hydrochloride by slow continuous infusion by a central line or through a large peripheral vein. Change the infusion site every 12 hours if administered via peripheral vein.

Inspection and Preparation
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the solution if particulate matter, precipitate, or crystallization is present, or if the container appears damaged.

Flexible Containers
Dilution is not required for Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection.

Check the container for minute leaks prior to use by squeezing the bag firmly; ensure that the seal is intact. If leaks are found, discard solution as sterility may be impaired.

Do not combine Nicardipine Hydrochloride in 0.9% Sodium Chloride Injection with any product in the same intravenous line or premixed container. Do not add supplementary medication to the bag. Protect from light until ready to use.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is complete.

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Dosage as a Substitute for Oral Nicardipine Therapy
The intravenous infusion rate required to produce an average plasma concentration equivalent to a given oral dose at steady state is shown in the table in the package insert.

Dosage for Initiation of Therapy in a Drug-Free Patient
The time course of blood pressure decrease is dependent on the initial rate of infusion and the frequency of dosage adjustment. Nicardipine hydrochloride injection is administered by slow continuous infusion at a concentration of 0.1 mg/mL.

Conditions Requiring Infusion Adjustment
Hypotension or Tachycardia: In case of hypotension or tachycardia, discontinue infusion. When blood pressure and heart rate stabilize, restart infusion at low doses such as 30 mL/hr to 50 mL/hr (3 mg/hr to 5 mg/hr) and titrate to maintain desired blood pressure.

Infusion Site Changes: Change infusion site every 12 hours if administered via peripheral vein.

Impaired Cardiac, Hepatic, or Renal Function: Monitor closely when titrating nicardipine hydrochloride injection in patients with congestive heart failure or impaired hepatic or renal function.

Transfer to Oral Antihypertensive Agents
If treatment includes transfer to an oral antihypertensive agent other than nicardipine capsules, initiate oral therapy upon discontinuation of nicardipine hydrochloride injection.

When switching to a TID regimen of nicardipine capsules, administer the first dose 1 hour prior to discontinuation of the infusion.

Overdosage
Based on results obtained in laboratory animals, lethal overdose may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdosage, standard measures including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned to avoid cerebral anoxia. Frequent blood pressure determinations are essential. Vasopressors are clinically indicated for patients exhibiting profound hypotension. Intravenous calcium gluconate may help reverse the effects of calcium entry blockade.

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.

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