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Press Release

Hikma launches Triazolam Tablets

London, 19 November 2018 – Hikma Pharmaceuticals PLC (Hikma, Group) (LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1 Moody's / BB+ S&P, both stable) announces that Hikma Pharmaceuticals USA Inc., formerly known as West-Ward Pharmaceuticals Corp., has launched Triazolam Tablets, 0.125mg and 0.25mg the generic equivalent to Halcion®.[1]

Hikma's Triazolam tablets are indicated for the short-term treatment of insomnia (generally seven to ten days). Use for more than two or three weeks requires complete reevaluation of the patient.

Prescriptions for triazolam tablets should be written for short-term use (seven to ten days) and it should not be prescribed in quantities exceeding a one-month supply.

According to IQVIA, US sales of Triazolam Tablets were approximately $27 million in the 12 months ending September 2018.

Brian Hoffmann, President, Generics Division, said, "We are excited to launch Triazolam Tablets, improving patients' access to this product. This launch highlights the successful execution of our strategy to develop more differentiated products by leveraging our specialised manufacturing capabilities."

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[1] Halcion® is a registered trademark of Pfizer

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About Hikma

Hikma helps put better health within reach every day for millions of people in more than 50 countries around the world. For 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. We're 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 8,500 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner in the MENA region, 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 Triazolam Tablets, 0.125mg and 0.25mg:

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

See full Prescribing Information for complete boxed warning.

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma and death.

- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Contraindications
Triazolam tablets are contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines.

Triazolam tablets are contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving triazolam tablets, she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

Triazolam tablets are contraindicated with medications that significantly impair the oxidating metabolism mediated by cytochrome P450 3A (CYP 3A) including ketoconazole, itraconazole, nefazone and several HIV protease inhibitors.

Risks from Concomitant Use with Opioids (see Boxed Warning)
Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe triazolam tablets concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of triazolam tablets than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking triazolam tablets, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when triazolam tablets are used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined.

Persistent or Worsening Insomnia
Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. **The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.** Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative-hypnotic drugs. Because some of the important adverse effects of sedative-hypnotics appear to be dose related, it is important to use the smallest possible effective dose, especially in the elderly.

"Sleep-driving" and Other Complex Behaviors
Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These events can occur in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as sleep-driving may occur with sedative-hypnotics alone at therapeutic doses, the use of alcohol and other CNS depressants with sedative-hypnotics appears to increase the risk of such behaviors, as does the use of sedative-hypnotics at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of sedative-hypnotics should be strongly considered for patients who report a "sleep-driving" episode.

Other complex behaviors (e.g., preparing and eating food, making phone calls or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with sleep-driving, patients usually do not remember these events.

Severe Anaphylactic and Anaphylactoid Reactions
Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including triazolam. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with triazolam should not be rechallenged with the drug.

Central Nervous System Manifestations
An increase in daytime anxiety has been reported for triazolam tablets after as few as 10 days of continuous use. In some patients this may be a manifestation of interdose withdrawal. If increased daytime anxiety is observed during treatment, discontinuation of treatment may be advisable.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine hypnotics including triazolam tablets. Some of these changes may be characterized by decreased inhibition, e.g., aggressiveness and extroversion that seem excessive, similar to that seen with alcohol and other CNS depressants (e.g., sedative/hypnotics). Other kinds of behavioral changes have also been reported, for example, bizarre behavior, agitation, hallucinations, depersonalization. In primarily depressed patients, the worsening of depression, including suicidal thinking, has been reported in association with the use of benzodiazepines. The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Because of its depressant CNS effects, patients receiving triazolam should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the concomitant ingestion of alcohol and other CNS depressant drugs during treatment with triazolam tablets.

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As with some, but not all benzodiazepines, anterograde amnesia of varying severity and paradoxical reactions have been reported following therapeutic doses of triazolam tablets. Data from several sources suggest that anterograde amnesia may occur at a higher rate with triazolam tablets than with other benzodiazepine hypnotics.

Triazolam Interactions With Drugs That Inhibit Metabolism via Cytochrome P450 3A
Triazolam should be avoided in patients receiving very potent inhibitors of CYP 3A. With drugs inhibiting CYP 3A to a lesser but still significant degree, triazolam should be used only with caution and consideration of appropriate dosage reduction. Examples of drugs known to inhibit the metabolism of triazolam and/or related benzodiazepines include ketoconazole, itraconazole, nefazodone, and several HIV protease inhibitors.

Precautions
Human studies have not been performed; however, studies in rats have indicated that triazolam and its metabolites are secreted in milk. Therefore, administration of triazolam tablets to nursing mothers is not recommended.

The elderly are especially susceptible to the dose related adverse effects of triazolam tablets. In elderly and/or debilitated patients it is recommended that treatment with triazolam tablets be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness or impaired coordination.

Some side effects reported in association with the use of triazolam tablets appear to be dose-related. These include drowsiness, dizziness, light-headedness and amnesia.

Cases of “traveler’s amnesia” have been reported by individuals who have taken triazolam tablets to induce sleep while traveling.

Caution should be exercised if triazolam tablets are prescribed to patients with signs or symptoms of depression that could be intensified by hypnotic drugs.

The usual precautions should be observed in patients with impaired renal or hepatic function, chronic pulmonary insufficiency, and sleep apnea.

Safety and effectiveness of triazolam tablets in individuals younger than 18 years of age have not been established.

Adverse Reactions
During placebo-controlled clinical studies in which 1,003 patients received triazolam tablets, the most troublesome side effects were extensions of the pharmacologic activity of triazolam, e.g., drowsiness, dizziness or light-headedness.

Untoward events occurring in ≥1% of patients receiving triazolam tablets (vs placebo) include: drowsiness: 14.0% (placebo: 6.4%), headache: 9.7% (placebo 8.4%), dizziness: 7.8% (placebo: 3.1%), nervousness: 5.2% (placebo: 4.5%), light-headedness: 4.9% (placebo: 0.9%), coordination disorders/ataxia: 4.6% (placebo: 0.8%) and nausea/vomiting: 4.6% (placebo: 3.7%). Note that these figures cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those in clinical trials.

In addition to the relatively common (i.e., 1% or greater) untoward events enumerated above, the following adverse events have been reported less frequently (i.e., 0.9% to 0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

In addition to these untoward events for which estimates of incidence are available, the following adverse events have been reported in association with the use of triazolam tablets and other benzodiazepines: amnestic symptoms (anterograde amnesia with appropriate or inappropriate behavior), confusional states (disorientation, derealization, depersonalization, and/or clouding of consciousness), dystonia, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention. Other factors may contribute to some of these reactions, e.g., concomitant intake of alcohol or other drugs, sleep deprivation, an abnormal premorbid state, etc.

Other events reported include: paradoxical reactions such as stimulation, mania, an agitational state (restlessness, irritability, and excitation), increased muscle spasticity, sleep disturbances, hallucinations, delusions, aggressiveness, falling, somnambulism, syncope, inappropriate behavior and other adverse behavioral effects. Should these occur, use of the drug should be discontinued.

The following events have also been reported: chest pain, burning tongue/glossitis/stomatitis.

When treatment with triazolam tablets is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable.

Interactions
When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation. In particular, triazolam produces additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs which themselves produce CNS depression. Co-administration of triazolam with with isoniazid, oral contraceptives, grapefruit juice, and ranitidine increased maximum plasma concentrations of triazolam.

Available data from clinical studies of benzodiazepines other than triazolam suggest a possible drug interaction with triazolam for the following: fluvoxamine, diltiazem, and verapamil. Data from *in vitro* studies of triazolam suggest a possible drug interaction with triazolam for the following: sertraline and paroxetine. Data from *in vitro* studies of benzodiazepines other than triazolam suggest a possible drug interaction with triazolam for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine.

Overdosage
Because of the potency of triazolam, some manifestations of overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg).

Manifestations of overdosage with triazolam tablets include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiratory depression and apnea have been reported with overdosages of triazolam tablets. Seizures have occasionally been reported after overdosages.

For more information, please see the full Prescribing Information, including Boxed Warning regarding risks from concomitant use with opioids, and the Medication Guide.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

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