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Press Release

Hikma launches Tetrabenazine Tablets

London, 13 September 2019 – Hikma Pharmaceuticals PLC (Hikma, Group) (LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated Ba1/stable Moody's and BB+/positive S&P) the multinational pharmaceutical company, has launched Tetrabenazine Tablets, 12.5mg and 25mg, the generic equivalent to Xenazine®[1], in the US through its US affiliate, Hikma Pharmaceuticals USA Inc.[2]

Tetrabenazine Tablets are a vesicular monoamine transporter 2 (VMAT) inhibitor indicated for the treatment of chorea associated with Huntington's disease.

According to IQVIA, US sales of Tetrabenazine Tablets, 12.5mg and 25mg, were approximately $119 million in the 12 months ending July 2019.

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Enquiries

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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 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'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 8,400 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.

[1] Xenazine® is a registered trademark of Lundbeck
[2] Hikma Pharmaceuticals USA Inc. was formerly known as West-Ward Pharmaceuticals Corp.

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Important Safety Information for Tetrabenazine Tablets, 12.5mg and 25mg:

BOXED WARNING:
WARNING: DEPRESSION AND SUICIDALITY
See full Prescribing Information

Tetrabenazine can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of tetrabenazine must balance the risks of depression and suicidality with the clinical need for control of chorea. Close observation of patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior should accompany therapy. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviors of concern promptly to the treating physician.

Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington's disease. Tetrabenazine is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.

Contraindications
Tetrabenazine is contraindicated in patients:

- Who are actively suicidal, or who have depression which is untreated or undertreated
- With hepatic impairment
- Taking monoamine oxidase inhibitors (MAOIs)
- Taking reserpine
- Taking deutetrabenazine or valbenazine

Warnings and Precautions
Depression and Suicidality
Patients with Huntington's disease are at increased risk for depression, suicidal ideation or behaviors (suicidality). Tetrabenazine increases the risk for suicidality in patients with Huntington's Disease.

When considering the use of tetrabenazine, the risk of suicidality should be balanced against the need for treatment of chorea. All patients treated with tetrabenazine should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with tetrabenazine.

Patients, their caregivers, and families should be informed of the risks of depression, worsening depression, and suicidality associated with tetrabenazine, and should be instructed to report behaviors of concern promptly to the treating physician. Patients with HD who express suicidal ideation should be evaluated immediately.

Clinical Worsening and Adverse Effects
Prescribers should periodically re-evaluate the need for tetrabenazine in their patients by assessing the effect on chorea and possible adverse effects, including depression and suicidality, cognitive decline, Parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness and disability.

Laboratory Tests
Tetrabenazine should be titrated slowly over several weeks and individualized for each patient. Before a dose >50 mg/day is administered, determine a patient's CYP2D6 metabolizer status. Individualize doses according to a patient's status. Do not exceed a dose of 50 mg/day or 25 mg/dose in poor metabolizers and when administering tetrabenazine with strong CYP2D6 inhibitors.

Tetrabenazine therapy should be re-titrated if there is a treatment interruption of >5 days.

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with tetrabenazine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis and acute renal failure.

The management of NMS should include immediate discontinuation of tetrabenazine, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Recurrence of NMS has been reported with resumption of drug therapy. If treatment with tetrabenazine is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Parkinsonism
Tetrabenazine can cause Parkinsonism. Drug-induced Parkinsonism has the potential to cause more functional disability than untreated chorea for some patients with Huntington's disease. If a patient develops Parkinsonism during treatment with tetrabenazine, dose reduction should be considered; in some patients, discontinuation of therapy may be necessary.

Akathisia, Restlessness, and Agitation
Tetrabenazine may increase the risk of akathisia, restlessness and agitation and can also cause other serious adverse reactions, including Parkinsonism. These adverse reactions may require a dose reduction or discontinuation of tetrabenazine.

Sedation and Somnolence
Tetrabenazine may induce sedation/somnolence, which may impair a patient's ability to drive or operate dangerous machinery. Concomitant use of alcohol or other sedating drugs can worsen sedation/somnolence. In some patients, sedation occurred at doses that were lower than recommended doses.

QTc Prolongation
Tetrabenazine causes a small prolongation of QTc (about 8 msec) and should not be used in combination with drugs known to prolong QTc (which in certain circumstances can lead to *torsades de pointes* and/or sudden death), in patients with congenital long QT syndrome or in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of *torsades de pointes* and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The risk of Parkinsonism, NMS and akathisia may be increased by concomitant use of tetrabenazine and dopamine antagonists or antipsychotics.

Hypotension and Orthostatic Hypotension
Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension.

Hyperprolactinemia
Tetrabenazine elevates serum prolactin concentrations. If symptomatic hyperprolactinemia is suspected, conduct appropriate laboratory testing and consider discontinuing tetrabenazine.

Binding to Melanin-Containing Tissues
Since tetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that tetrabenazine may cause toxicity in these tissues after extended use. Opthalmologic monitoring in humans was inadequate to exclude the possibility of injury occurring after long-term exposure.

Adverse Events
Some adverse events, such as akathisia, restlessness, agitation, Parkinsonism, depression, insomnia, anxiety or sedation, may be dose-dependent. Stop titration and reduce the dose of tetrabenazine if observed. If the adverse reaction does not resolve, consider withdrawing tetrabenazine or initiating other specific treatment.

The most commonly reported adverse reactions with tetrabenazine (>10% and at least 5% greater than placebo) were sedation/somnolence (31% vs 3%), insomnia (22% vs 0%), fatigue (22% vs 13%), depression (19% vs 0%), akathisia (19% vs 0%), anxiety/anxiety aggravated (15% vs 3%) and nausea (13% vs 7%).

<u>Drug Interactions</u>
Tetrabenazine tablets are contraindicated for use with monoamine oxidase inhibitors (MAOIs), reserpine, and deutetrabenazine or valbenazine.

- Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) markedly increase exposure to these metabolites. A reduction in tetrabenazine dose may be necessary when adding a strong CYP2D6 inhibitor

- Tetrabenazine and reserpine should not be used concomitantly. At least 20 days should elapse after stopping reserpine before starting tetrabenazine.
- Tetrabenazine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI
- Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence
- Tetrabenazine causes a small prolongation of QTc (about 8 msec), concomitant use with other drugs that are known to cause QTc prolongation should be avoided, these including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval.
- The risk for Parkinsonism, NMS, and akathisia may be increased by concomitant use of tetrabenazine and dopamine antagonists or antipsychotics (e.g., chlorpromazine, haloperidol, olanzapine, risperidone, thioridazine, ziprasidone)
- Tetrabenazine is contraindicated in patients currently taking deutetrabenazine or valbenazine.

For more information, please see the Medication Guide and full Prescribing Information, including the Boxed Warning for depression and suicidality.

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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