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Press Release

Hikma launches Levothyroxine Sodium Injection in ready-to-use vials

London, 14 December 2022 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Levothyroxine Sodium Injection in the US. The product is available in ready-to-use vials in a 100mcg/mL dose. Levothyroxine Sodium is an important medicine used in hospitals for the treatment of myxedema coma.

According to IQVIA, US sales of Levothyroxine Sodium Injection, 100mcg/mL, were approximately $52 million in the 12 month period ending September 2022.

Hikma is a top three supplier of generic injectable medicines by volume in the US.[1] In 2022, Hikma has launched 11 new injectable products, taking its total injectable portfolio to over 130 products.

Riad Mishlawi, President of Injectables said, "We are pleased to launch Levothyroxine Sodium Injection in a more concentrated, ready-to-use formulation. This launch, which came to us through the Custopharm acquisition, broadens the choice of medicines available to hospitals, helping us to ensure that we are providing affordable and accessible medicines to those in need. We are committed to expanding our portfolio of essential medicines that serve the growing needs of US medical professionals."

- ENDS -

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

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 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

[1] Source: IQVIA MAT through September 2022, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson.

branded and non-branded generic medicines. Together, our 8,700 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 Levothyroxine Sodium Injection, 100mcg/mL:

BOXED WARNING

WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS

Thyroid hormones, including Levothyroxine Sodium Injection, should not be used for the treatment of obesity or for weight loss. (5.3)

Larger doses may produce serious or even life-threatening manifestations of toxicity. (6)

CONTRAINDICATIONS

None

WARNINGS & PRECAUTIONS

- **Risk of Cardiac Complications in Elderly and in Patients with Cardiovascular Disease –** Excessive bolus dosing of Levothyroxine Sodium Injection (greater than 500 mcg) is associated with cardiac complications, particularly in the elderly and in patients with an underlying cardiac condition. Adverse events that can potentially be related to the administration of large doses of Levothyroxine Sodium Injection include arrhythmias, tachycardia, myocardial ischemia and infarction, or worsening of congestive heart failure and death. Cautious use, including doses in the lower end of the recommended range, may be warranted in these populations. Close observation of the patient following the administration of Levothyroxine Sodium Injection is advised.
- **Acute Adrenal Crisis in Patients with Concomitant Adrenal Insufficiency –** Chronic autoimmune thyroiditis, which can lead to myxedema coma, may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Patients should be treated with replacement glucocorticoids prior to initiation of treatment with Levothyroxine Sodium Injection, until adrenal function has been adequately assessed. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. With initiation of Levothyroxine Sodium Injection, patients with myxedema coma should also be monitored for previously undiagnosed diabetes insipidus.
- **Worsening of Diabetic Control –** Addition of levothyroxine therapy in patients with diabetes mellitus may worsen glycemic control and result in increased antidiabetic agent or insulin requirements. Carefully monitor glycemic control *[see Drug Interactions (7.1)]*.

ADVERSE REACTIONS

Adverse reactions associated with levothyroxine are primarily those of hyperthyroidism due to therapeutic overdosage *[see Warnings and Precautions (5), Overdosage (10)]*. They include the following:

- *General:* fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating
- *Central nervous system:* headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia
- *Musculoskeletal:* tremors, muscle weakness, muscle spasm
- *Cardiovascular:* palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest
- *Respiratory:* dyspnea
- *Gastrointestinal:* diarrhea, vomiting, abdominal cramps, elevations in liver function tests
- *Dermatologic:* flushing, rash

Seizures have been reported rarely with the institution of levothyroxine therapy.

Hypersensitivity Reactions

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various gastrointestinal symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness, and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

DRUG INTERACTIONS

Drugs Known to Affect Thyroid Hormone Pharmacokinetics
Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to Levothyroxine Sodium Injection (see Tables 1-3 of the package insert).

Antidiabetic Therapy
Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended.

Oral Anticoagulants
Levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid. Closely monitor coagulation tests to permit appropriate and timely dosage adjustments.

Digitalis Glycosides
Levothyroxine may reduce the therapeutic effects of digitalis glycosides. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides.

Antidepressant Therapy
Concurrent use of tricyclic (e.g., amitriptyline) or tetracyclic (e.g., maprotiline) antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and central nervous system stimulation. Levothyroxine may accelerate the onset of action of tricyclics. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.

Ketamine
Concurrent use of ketamine and levothyroxine may produce marked hypertension and tachycardia. Closely monitor blood pressure and heart rate in these patients.

Sympathomimetics
Concurrent use may of sympathomimetics and levothyroxine may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.

Drug-Laboratory Test Interactions
Consider changes in TBG concentration when interpreting T4 and T3 values. Measure and evaluate unbound (free) hormone and/or determine the free T4 index (FT4I) in this circumstance. Pregnancy, infectious hepatitis, estrogens, estrogen containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, androgens, and corticosteroids decrease TBG concentration. Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
The clinical data in pregnant women treated with oral levothyroxine to treat hypothyroidism do not indicate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no data available on the use of Levothyroxine Sodium Injection in pregnant women. There are risks to the mother and fetus associated with myxedema coma in pregnancy *(see Clinical Considerations)*.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk
Myxedema coma is a medical emergency that can be fatal if left untreated. Delaying treatment in pregnant women with myxedema coma increases the risk of maternal and fetal morbidity and mortality. Life-sustaining therapy for pregnant women with myxedema coma should not be withheld due to potential concerns regarding the effects of Levothyroxine Sodium Injection on the fetus.

Lactation
Risk Summary
Published studies report that levothyroxine is present in human milk following the administration of oral levothyroxine. No adverse effects on the breastfed infant have been reported, and there is no information on the effects of levothyroxine on milk production from levothyroxine oral treatment. There are no available data with use of Levothyroxine Sodium Injection in lactating women. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Levothyroxine Sodium Injection and any potential adverse effects on the breastfed infant from Levothyroxine Sodium Injection or from the underlying maternal condition.

Pediatric Use
The safety and effectiveness of Levothyroxine Sodium Injection have not been established in pediatric patients.

Geriatric Use and Patients with Underlying Cardiovascular Disease
See Section 2, Dosage and Administration, for full prescribing information in the geriatric patient population. Because of the increased prevalence of cardiovascular disease in the elderly, cautious use of Levothyroxine Sodium Injection in the elderly and in patients with known cardiac risk factors is advised. Atrial fibrillation is a common side effect associated with levothyroxine treatment in the elderly *[see Dosage and Administration (2) and Warnings and Precautions (5)].*

Renal Impairment
Serum creatinine and levothyroxine levels should be closely monitored in patients with severe renal impairment receiving intravenous levothyroxine with betadex sulfobutyl (SBECD) *[See Clinical Pharmacology (12.3)].*

DOSAGE AND ADMINISTRATION

Dosage
An initial intravenous loading dose of Levothyroxine Sodium Injection between 300 to 500 mcg, followed by once daily intravenous maintenance doses between 50 and 100 mcg, should be administered, as clinically indicated, until the patient can tolerate oral therapy.

The age, general physical condition, and cardiac risk factors of the patient, as well as the clinical severity of myxedema and duration of myxedema symptoms should be considered when determining the starting and maintenance dosages of Levothyroxine Sodium Injection.

Levothyroxine Sodium Injection produces a gradual increase in the circulating concentrations of the hormone with an approximate half-life of 9 to 10 days in hypothyroid patients. Daily administration of Levothyroxine Sodium Injection should be maintained until the patient is capable of tolerating an oral dose and is clinically stable. For chronic treatment of hypothyroidism, an oral dosage form of levothyroxine should be used to maintain a euthyroid state. Relative bioavailability between Levothyroxine Sodium Injection and oral levothyroxine products has not been established. Based on medical practice, the relative bioavailability between oral and intravenous administration of Levothyroxine Sodium Injection is estimated to be from 48 to 74%. Due to differences in absorption characteristics of patients and the oral levothyroxine product formulations, TSH and thyroid hormone levels should be measured a few weeks after initiating oral levothyroxine and dose adjusted accordingly.

Dosing in the Elderly and in Patients with Cardiovascular Disease
Intravenous levothyroxine may be associated with cardiac toxicity – including arrhythmias, tachycardia, myocardial ischemia and infarction, or worsening of congestive heart failure and death – in the elderly and in those with underlying cardiovascular disease. Therefore, cautious use, including doses in the lower end of the recommended range, may be warranted in these populations.

Administration Instructions
Intravenous levothyroxine may be associated with cardiac toxicity including arrhythmias, tachycardia, myocardial ischemia and infarction, or worsening of congestive heart failure and death – in the elderly and in those with

underlying cardiovascular disease. Therefore, cautious use, including doses in the lower end of the recommended range, may be warranted in these populations.

Discard any unused portion. DO NOT ADD LEVOTHYROXINE SODIUM INJECTION TO OTHER INTRAVENOUS FLUIDS. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

OVERDOSAGE

In general, the signs and symptoms of overdosage with levothyroxine are those of hyperthyroidism *[see Warnings and Precautions (5) and Adverse Reactions (6)].* In addition, confusion and disorientation may occur. Cerebral embolism, shock, coma, and death have been reported. Excessive doses of Levothyroxine Sodium Injection (greater than 500 mcg) are associated with cardiac complications in patients with underlying cardiac disease.

Treatment of Overdosage
Levothyroxine Sodium Injection should be reduced in dose or temporarily discontinued if signs or symptoms of overdosage occur. To obtain up-to-date information about the treatment of overdose, a good resource is the certified Regional Poison Control Center. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in the patient.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's medical status.

INDICATIONS AND USAGE

Levothyroxine Sodium Injection is indicated for the treatment of myxedema coma.

Limitations of Use: The relative bioavailability between Levothyroxine Sodium Injection and oral levothyroxine products has not been established. Caution should be used when switching patients from oral levothyroxine products to Levothyroxine Sodium Injection as accurate dosing conversion has not been studied.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
Levothyroxine Sodium Injection 100 mcg/mL is a clear, colorless to slightly yellow solution, supplied as1 mL per vial.

Package of 1 single-dose vial: NDC 24201-002-01

Storage and Handling
Protect from light and store product at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Drug product is preservative free. Discard any unused portion.

ENDING INFORMATION

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

To report SUSPECTED ADVERSE REACTIONS, contact Leucadia Pharmaceuticals at 1-877-411-9681 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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