Press Release

Hikma receives FDA approval and launches Mercaptopurine Oral Suspension in the US

London, 27 February 2025 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has received FDA approval for and launched Mercaptopurine Oral Suspension, in a 20mg/mL dose in the US. Hikma is introducing the first generic of this product, and was the first approved applicant with a Competitive Generic Therapy (CGT) designation from the US Food and Drug Administration. Therefore, Hikma is eligible for 180 days of CGT exclusivity.

Mercaptopurine Oral Suspension is indicated for the treatment of patients with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen. According to IQVIA, US sales of Mercaptopurine Oral Suspension, 20mg/mL, were approximately $14 million in the 12 months ending December 2024.

Hafrun Fridriksdottir, President of Hikma's Generics business, said: "We are proud to introduce the first generic of Mercaptopurine Oral Suspension to patients in the US. Developed by our internal R&D team, this launch demonstrates our commitment to improving patient access to high-quality medicines."

Hikma's Generic business supplies a range of oral, inhalation and other generic and specialty products in the US market, and has expertise in complex technologies, such as nasal sprays, where we are the largest supplier by volume in the US[1].

- ENDS –

This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

Enquiries

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

Hikma helps put better health within reach every day for millions of people around the world. For more than 45 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 North America, 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

[1] IQVIA MAT December 2024, volumes by eaches

non-branded generic medicines. Together, our 9,100 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 MERCAPTOPURINE ORAL SUSPENSION

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

- **Myelosuppression**

The most consistent, dose-related adverse reaction of mercaptopurine is myelosuppression, manifested by anemia, leukopenia, thrombocytopenia or any combination of these. Monitor complete blood counts (CBC) and adjust the dosage for excessive myelosuppression.

Consider testing for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency in patients with severe myelosuppression or repeated episodes of myelosuppression. Patients with homozygous TPMT or NUDT15 deficiency may require a dose reduction.

Myelosuppression can be exacerbated by coadministration with allopurinol, aminosalicylates or other products that cause myelosuppression. Reduce the dosage of mercaptopurine when coadministered with allopurinol.

- **Hepatotoxicity**

Mercaptopurine is hepatotoxic. There are reports of deaths attributed to hepatic necrosis associated with the administration of mercaptopurine. Hepatic injury can occur with any dosage but seems to occur with greater frequency when the recommended dosage is exceeded. In some patients, jaundice has cleared following withdrawal of mercaptopurine and reappeared with rechallenge.

Usually, clinically detectable jaundice appears in the first or second month of treatment; however, jaundice has been reported as early as 1 week and as late as 8 years after starting mercaptopurine. Hepatic encephalopathy has occurred.

Monitor serum transaminase levels, alkaline phosphatase and bilirubin levels at weekly intervals when first beginning therapy and at monthly intervals thereafter. Monitor liver tests more frequently in patients who are receiving mercaptopurine with other hepatotoxic drugs or with known pre-existing liver disease. Withhold mercaptopurine at onset of hepatotoxicity.

Intrahepatic Cholestasis of Pregnancy
Postmarketing cases of intrahepatic cholestasis of pregnancy (ICP) have been reported in patients with inflammatory bowel disease (IBD) who received mercaptopurine during pregnancy. Discontinue mercaptopurine if ICP develops in a pregnant woman.

- **Immunosuppression**

Mercaptopurine is immunosuppressive and may impair the immune response to infectious agents or vaccines. Due to the immunosuppression associated with maintenance chemotherapy for acute lymphoblastic leukemia (ALL), response to all vaccines may be diminished and there is a risk of infection with live virus vaccines. Consult immunization guidelines for immunocompromised patients.

- **Treatment-Related Malignancies**

Mercaptopurine is mutagenic in animals and humans, carcinogenic in animals and may increase the risk of secondary malignancies. Hepatosplenic T-cell lymphoma has been reported in patients treated with mercaptopurine for IBD, an unapproved use.

Patients receiving immunosuppressive therapy, including mercaptopurine, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers, sarcomas and uterine cervical cancer in situ. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants should therefore be used with caution, as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly, increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

- **Macrophage Activation Syndrome**

Macrophage activation syndrome (MAS) (hemophagocytic lymphohistiocytosis) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with IBD, and there could potentially be an increased susceptibility for developing the condition with the use of mercaptopurine (an unapproved use). If MAS occurs, or is suspected, discontinue mercaptopurine. Monitor for and promptly treat infections such as EBV and cytomegalovirus, as these are known triggers for MAS.

- **Embryo-Fetal Toxicity**

Mercaptopurine can cause fetal harm when administered to a pregnant woman. An increased incidence of miscarriage has been reported in women who received mercaptopurine in the first trimester of pregnancy. Adverse embryo-fetal findings, including miscarriage and stillbirth, have been reported in women who received mercaptopurine after the first trimester of pregnancy. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with mercaptopurine and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with mercaptopurine and for 3 months after the last dose.

- **Risks in Patients With Phenylketonuria**

Patients with phenylketonuria should be informed that mercaptopurine oral suspension contains phenylalanine.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in the Full Prescribing Information:

- Myelosuppression
- Hepatotoxicity
- Immunosuppression
- Treatment-Related Malignancies
- MAS

Based on multicenter cooperative group ALL trials, the most common adverse reaction occurring in >20% of patients was myelosuppression. Adverse reactions occurring in 5% to 20% of patients included anorexia, nausea, vomiting, diarrhea, malaise and rash. Delayed or late toxicities include hepatic fibrosis, hyperbilirubinemia, alopecia, pulmonary fibrosis, oligospermia and secondary malignancies.

Drug fever has been reported with mercaptopurine.

Adverse reactions identified during postapproval use of mercaptopurine include photosensitivity, hypoglycemia, portal hypertension, ICP, pellagra and erythema nodosum.

DRUG INTERACTIONS

- **Allopurinol**

Reduce the dose of mercaptopurine when coadministered with allopurinol.

- **Warfarin**

The coadministration of mercaptopurine with warfarin may decrease the anticoagulant effectiveness of warfarin. Monitor the international normalized ratio (INR) in patients receiving warfarin and adjust the warfarin dosage as appropriate.

- **Myelosuppressive Products**

Mercaptopurine can cause myelosuppression, which may be increased when it is coadministered with other drugs that cause myelosuppression. Enhanced myelosuppression has been noted in some patients receiving trimethoprim-sulfamethoxazole. Monitor the CBC and adjust the dose of mercaptopurine for excessive myelosuppression.

- **Aminosalicylates**

Aminosalicylates may inhibit the TPMT enzyme, which may increase the risk of myelosuppression when coadministered with mercaptopurine. When aminosalicylates and mercaptopurine are coadministered, use the lowest possible doses for each drug and monitor more frequently for myelosuppression.

- **Hepatotoxic Products**

Mercaptopurine can cause hepatotoxicity, which may be increased when coadministered with other products that cause hepatotoxicity. Monitor liver tests more frequently in patients who are receiving mercaptopurine with other hepatotoxic products.

- **Methotrexate**

Mercaptopurine dosage may need adjustment when administered concomitantly with high-dose methotrexate. Mercaptopurine exposure increases with concomitant methotrexate use, which may increase the risk of mercaptopurine adverse reactions.

USE IN SPECIFIC POPULATIONS

- **Pregnancy**

Mercaptopurine can cause fetal harm when administered to a pregnant woman. Pregnant women who receive mercaptopurine have an increased incidence of miscarriage and stillbirth. Advise pregnant women of the potential risk to a fetus.

- **Lactation**

Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with mercaptopurine and for 1 week after the last dose.

- **Females and Males of Reproductive Potential**

Mercaptopurine can cause fetal harm when administered to pregnant women.

Verify pregnancy status in females of reproductive potential prior to initiating mercaptopurine.

Advise females of reproductive potential to use effective contraception during treatment with mercaptopurine and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with mercaptopurine and for 3 months after the last dose.

- **Pediatric Use**

Symptomatic hypoglycemia has been reported in pediatric patients with ALL receiving mercaptopurine.

- **Geriatric Use**

Clinical studies of mercaptopurine 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. 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 of concomitant disease or another drug therapy.

- **Renal Impairment**

Use the lowest recommended starting dosage for mercaptopurine or increase the dosing interval to every 36 to 48 hours in patients with renal impairment. Adjust the dose to maintain absolute neutrophil count (ANC) at a desirable level and for adverse reactions.

- **Hepatic Impairment**

Use the lowest recommended starting dosage for mercaptopurine in patients with hepatic impairment. Adjust the dose to maintain ANC at a desirable level and for adverse reactions.

OVERDOSAGE

Signs and symptoms of mercaptopurine overdosage may be immediate (anorexia, nausea, vomiting and diarrhea) or delayed (myelosuppression, liver dysfunction and gastroenteritis). Dialysis cannot be expected to clear mercaptopurine. Hemodialysis is thought to be of marginal use due to the rapid intracellular incorporation of mercaptopurine into active metabolites with long persistence.

Withhold mercaptopurine immediately if severe or life-threatening adverse reactions occur during treatment. If a patient is seen immediately following an accidental overdosage, it may be useful to induce emesis.

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PATIENT COUNSELING INFORMATION
Advise patients and caregivers to read the FDA-approved patient labelling. Advise patients and caregivers that mercaptopurine can cause myelosuppression, hepatotoxicity and gastrointestinal toxicity. Advise patients to contact their healthcare provider if they experience fever, sore throat, jaundice, nausea, vomiting, signs of local infection, bleeding from any site or symptoms suggestive of anemia.

Advise patients or caregivers on proper handling, storage, preparation, administration and disposal and clean-up of accidental spillage of the medication prior to initiation and on each visit to the clinic.

For more information, please see the Full Prescribing Information for Mercaptopurine Oral Suspension.

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

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