Press Release

Hikma launches Furosemide Injection, USP, in the US

London, 9 December 2024 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Furosemide Injection, USP, in 20mg/2mL, 40mg/4mL, 100mg/10mL, 500mg/50mL and 1,000mg/100mL presentations in the US. Hikma is introducing the first FDA approved 50mL and 100mL presentations to the US market and we are pleased to expand our portfolio with this launch, broadening the choice of medicines available to hospitals.

Furosemide Injection, USP is indicated in adults and pediatric patients for the treatment of edema associated with heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. It is also indicated as adjunctive therapy in acute pulmonary edema.

According to IQVIA, US sales of Furosemide Injection, USP, 20mg/2mL, 40mg/4mL and 100mg/10mL were approximately $30 million in the 12 months ending September 2024.

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 160 products. We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care.

- 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.

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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 the 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

[1] Source: IQVIA MAT September 2024, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

hikma.

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 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 Furosemide Injection, USP, 20mg/2mL, 40mg/4mL, 100mg/10mL, 500mg/50mL and 1,000mg/100mL:

Please see package insert for referenced section/section numbering, where appropriate.

CONTRAINDICATIONS

Furosemide injection is contraindicated in patients with anuria. Furosemide injection is contraindicated in patients with a history of hypersensitivity to furosemide.

WARNINGS & PRECAUTIONS

- **Fluid, Electrolyte, and Metabolic Abnormalities –** Furosemide may cause fluid, electrolyte, and metabolic abnormalities such as hypovolemia, hypokalemia, azotemia, hyponatremia, hypochloremic alkalosis, hypomagnesemia, hypocalcemia, hyperglycemia, or hyperuricemia, particularly in patients receiving higher doses, patients with inadequate oral electrolyte intake, and in elderly patients.
- **Worsening Renal Function –** Furosemide can cause dehydration and azotemia. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, furosemide should be discontinued. Furosemide use in the first year of life, especially in patients born pre-term, may precipitate nephrocalcinosis/nephrolithiasis.
- **Ototoxicity –** Cases of tinnitus and reversible or irreversible hearing impairment and deafness have been reported. Reports usually indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, the use of higher than recommended doses, hypoproteinemia or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs. Hearing loss in neonates, including premature neonates has been associated with the use of Furosemide injection.
- **Acute Urinary Retention –** In patients with severe symptoms of urinary retention (because of bladder emptying disorders, prostatic hyperplasia, urethral narrowing), the administration of furosemide can cause acute urinary retention related to increased production and retention of urine.

ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:
- Fluid, Electrolyte, and Metabolic Abnormalities *[see Warnings and Precautions (5.1)]*
- Ototoxicity *[see Warnings and Precautions (5.3)]*

The following adverse reactions associated with the use of furosemide were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions are categorized below by organ system and listed by decreasing severity.

Gastrointestinal System Reactions: pancreatitis, jaundice (intrahepatic cholestatic jaundice), increased liver enzymes, anorexia, oral and gastric irritation, cramping, diarrhea, constipation, nausea, vomiting. *Systemic Hypersensitivity Reactions:* severe anaphylactic or anaphylactoid reactions (e.g., with shock).
Systemic Hypersensitivity Reactions: systemic vasculitis, interstitial nephritis, necrotizing angiitis.
Central Nervous System Reactions: tinnitus and hearing loss, paresthesias, vertigo, dizziness, headache, blurred vision, xanthopsia.
Hematologic Reactions: aplastic anemia, thrombocytopenia, agranulocytosis, hemolytic anemia, leukopenia, anemia, eosinophilia.
Dermatologic-Hypersensitivity Reactions: toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, drug rash with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, exfoliative dermatitis, bullous pemphigoid, purpura, photosensitivity, rash.

Cardiovascular Reactions: orthostatic hypotension, increase in cholesterol and triglyceride serum levels.
Other Reactions: glycosuria, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis, transient injection site pain following intramuscular injection, fever.

DRUG INTERACTIONS

Effects of Furosemide on Other Drugs
Aminoglycoside antibiotics: Furosemide may increase the ototoxic potential of aminoglycoside antibiotics.
Ethacrynic acid: Possibility of ototoxicity.
Salicylates: May experience salicylate toxicity at lower doses because of competitive renal excretory sites.
Cisplatin: There is a risk of ototoxic effects if cisplatin and furosemide are given concomitantly.
Cisplatin and nephrotoxic drugs: Nephrotoxicity.
Paralytic agents: Furosemide has a tendency to antagonize the skeletal muscle relaxing effect of tubocurarine and may potentiate the action of succinylcholine.
Lithium: Furosemide reduces lithium's renal clearance and add a high-risk of lithium toxicity.
Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers: May lead to severe hypotension and deterioration in renal function, including renal failure.
Antihypertensive drugs: Furosemide may add to or potentiate the therapeutic effect of other antihypertensive drugs.
Adrenergic blocking drugs or peripheral adrenergic blocking drugs: Potentiation occurs.
Norepinephrine: Furosemide may decrease arterial responsiveness (vasoconstricting effect) to norepinephrine.
Chloral hydrate: In isolated cases, intravenous administration of furosemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure, and tachycardia.
Methotrexate and other drugs undergoing renal tubular secretion: Furosemide may decrease renal elimination of other drugs that undergo tubular secretion. High-dose treatment of furosemide may result in elevated serum levels of these drugs and may potentiate their toxicity.
Cephalosporin: Furosemide can increase the risk of cephalosporin-induced nephrotoxicity even in the setting of minor or transient renal impairment.
Cyclosporine: Increased risk of gouty arthritis secondary to furosemide-induced hyperuricemia and cyclosporine impairment of renal urate excretion.
Thyroid hormones: High-doses (> 80 mg) of furosemide may inhibit the binding of thyroid hormones to carrier proteins and result in transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels.

Effects of Other Drugs on Furosemide
Phenytoin: Interferes directly with renal action of furosemide.
Methotrexate and other drugs undergoing renal tubular secretion: May reduce the effect of furosemide. High-dose treatment of methotrexate and these other drugs may result in elevated serum levels of furosemide and may potentiate the toxicity of furosemide.
Indomethacin: Coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of furosemide in some patients by inhibiting prostaglandin synthesis. Indomethacin may also affect plasma renin levels, aldosterone excretion, and renin profile evaluation.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Available data from published observational studies, case reports, and postmarketing reports, from decades of use, have not demonstrated a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes with furosemide use during pregnancy. Untreated congestive heart failure and cirrhosis of the liver can lead to adverse outcomes for the mother and the fetus.

Lactation
Risk Summary
The presence of furosemide has been reported in human milk. There are no data on the effects on the breastfed infant or the effects on milk production. Doses of furosemide associated with clinically significant diuresis may impair milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for furosemide and any potential adverse effects on the breastfed infant from furosemide or from the underlying maternal condition.

Pediatric Use

Published reports indicate that premature infants with post conceptual age (gestational plus postnatal) less than 31 weeks receiving doses exceeding 1 mg/kg/24 hours may develop plasma levels which could be associated with potential toxic effects including ototoxicity. Furosemide in the first year of life, especially in patients born pre-term, may precipitate nephrocalcinosis/nephrolithiasis.

Geriatric Use
Controlled clinical studies of furosemide 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 the 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 other drug therapy.

DOSAGE AND ADMINISTRATION

General Considerations
Inspect Furosemide injection visually for particulate matter and discoloration before administration. Discard unused portion.

Recommended Dosage for Adults
Edema
Individualize therapy according to patient response. The usual initial dose of furosemide is 20 mg to 40 mg given as a single-dose, injected intramuscularly or intravenously. Give the intravenous dose slowly (over 1 minute to 2 minutes). If needed, administer another dose in the same manner 2 hours later or increase the dose. The dose may be raised by 20 mg and administered not sooner than 2 hours after the previous dose until the desired diuretic effect has been obtained. Administer this individually determined single-dose once or twice daily. Furosemide may also be administered via continuous intravenous infusion at a rate not greater than 4 mg/min.

Acute Pulmonary Edema
The usual initial dose of furosemide is 40 mg injected slowly intravenously (over 1 minute to 2 minutes). If a satisfactory response does not occur within 1 hour, increase the dose to 80 mg injected slowly intravenously (over 1 minute to 2 minutes).

Recommended Dosage for Pediatric Patients
The usual initial dose of Furosemide injection (intravenously or intramuscularly) in pediatric patients is 1 mg/kg body weight administered slowly (over 1 minute to 2 minutes). If the diuretic response to the initial dose is not satisfactory, dosage may be increased by 1 mg/kg not sooner than 2 hours after the previous dose, until the desired diuretic effect has been obtained. Doses greater than 6 mg/kg body weight are not recommended. The maximum dose for premature infants should not exceed 1 mg/kg/day.

OVERDOSAGE

The principal signs and symptoms of overdose with furosemide are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalemia and hypochloremic alkalosis, and are extensions of its diuretic action.

The concentration of furosemide in biological fluids associated with toxicity or death is not known. Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level, and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy). Hemodialysis does not accelerate furosemide elimination.

INDICATIONS AND USAGE

Edema
Furosemide injection is indicated in adults and pediatric patients for the treatment of edema associated with heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

Acute Pulmonary Edema
Furosemide injection is indicated as adjunctive therapy in acute pulmonary edema.

HOW SUPPLIED/STORAGE AND HANDLING

Unit of Sale	Presentations	Strength
NDC 0143-9155-25	Box of 25 amber glass single-dose vials	20 mg/2 mL (10 mg/mL)
NDC 0143-9156-10	Box of 10 amber glass single-dose vials	40 mg/4 mL (10 mg/mL)
NDC 0143-9157-10	Box of 10 amber glass single-dose vials	100 mg/10 mL (10 mg/mL)
NDC 0143-9158-01	Box of 1 clear glass single-dose vial with hanger	500 mg/50 mL (10 mg/mL)
NDC 0143-9159-01	Box of 1 clear glass single-dose vial with hanger	1,000 mg/100 mL (10 mg/mL)

Furosemide Injection is a sterile, colorless solution for injection, available as a single-dose vial that contains 10 mg/mL of furosemide, and is supplied as follows:

Discard unused portion. Do not use if solution is discolored or contains particulate.

2 mL, 4 mL and 10 mL amber glass single-dose vials:
Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature]. Protect from light.

50 mL and 100 mL clear glass single-dose vials:
Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature]. Protect from light. Retain in carton until contents are used.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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Distributed by:
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Document Identification Number: HK-2675-v1