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Press Release

Hikma Pharmaceuticals Receives Permanent J-Code for COMBOGESIC® IV (acetaminophen and ibuprofen) injection from Centers for Medicare & Medicaid Services (CMS)

Non-Opioid COMBOGESIC® IV Provides Shorter Onset to Analgesia*, Superior Analgesia Efficacy, Comparable Safety in Common AEs, and Sustained Pain Management Results[1†]

London 16 July 2024 -- Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces the U.S. Centers for Medicare and Medicaid Services (CMS) has assigned a unique, permanent Healthcare Common Procedure Coding System (HCPCS) J-code for COMBOGESIC® IV, an IV fixed dose combination (FDC) (acetaminophen and ibuprofen), non-opioid analgesia in a single formulation for adult pain management.[2] The new J-code **J0138**, which was assigned on July 5, 2024, will be effective October 1, 2024.[‡]

COMBOGESIC® IV is the first U.S. Food and Drug Administration-approved treatment for use in adults where an intravenous route of administration is considered clinically necessary for: (i) the relief of mild to moderate pain; or (ii) the management of moderate to severe pain as an adjunct to opioid analgesics.[2] COMBOGESIC® IV is an intravenous, opioid-free pain relief medicine that is a combination of 1,000 mg of acetaminophen and 300 mg of ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID).[2]

COMBOGESIC® IV offers health care providers an advanced, non-opioid approach to pain management by combining active drug substances with different mechanisms of action in a single formulation,[2] providing:

- Shorter onset to analgesia[1*]
- Superior analgesia efficacy and comparable safety in common adverse events[1]
- Sustained pain-management results[1†]

In a Phase 3 clinical trial (https://pubmed.ncbi.nlm.nih.gov/31447129/), COMBOGESIC® IV provided more than double the pain relief than that of acetaminophen IV and ibuprofen IV alone.[1] Time to meaningful pain relief was shorter in the COMBOGESIC® IV group than that in the Ibuprofen IV or placebo groups.[1] COMBOGESIC® IV also allows for superior analgesia efficacy with comparable safety in common AEs.[1]

“As an aesthetic plastic surgeon in practice for over 20 years, I take pride in not only providing each one of my patients with the best surgical outcome, but also the best overall recovery experience. An important component of that experience starts with pain reduction in the recovery room, and I have found that the use of COMBOGESIC® IV as a non-opioid pain analgesia has been a very effective treatment option. My patients appear more comfortable upon awakening, require less opioid use, can be discharged from our ambulatory surgery center more easily, and transition more smoothly to their recommended post-op oral pain regimen,” stated Alexander P. Moya, M.D., ASPS, ASAPS, a board-certified plastic surgeon, Lewisburg, Pennsylvania.

“We are pleased with the COMBOGESIC® IV J-Code assignment, as it will aid healthcare providers in billing and reimbursement, better supporting patient access to treatment for adult pain management,” said Dr. Bill Larkins, President of Injectables, Hikma. “We are grateful for the opportunity to provide non-opioid pain relief to so many patients around the country.”

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*Time to meaningful pain relief and onset time to analgesia were shorter in the COMBOGESIC® IV group than in the ibuprofen IV and placebo groups.

[†]A superior analgesic effect of COMBOGESIC® IV was observed during a single dosing interval ($SPID_6$ and $TOTPAR_6$) and at most scheduled time points according to VAS pain intensity, Pain Intensity Differences, and Pain Relief scores.

[‡]COMBOGESIC® IV is associated with a specific HCPCS Level II J-Code. This code is used to indicate drug administration and to determine how medical providers are reimbursed by payors. Standardized codes are utilized to ensure consistency across all payer groups, which helps to reduce the likelihood of billing errors.

About COMBOGESIC® IV
COMBOGESIC® IV is the only IV analgesic therapy formulated with 1,000 mg of acetaminophen and 300 mg of ibuprofen, utilizing the synergistic effect of both medicines for optimal pain relief.[2] It offers health care providers an advanced approach to multimodal analgesia by combining active drug substances with different mechanisms of action that harness additive or synergistic effects to provide more effective pain relief compared with individual components used as single-modality interventions.[1-3] COMBOGESIC® IV is supplied as a readily available solution with no mixing required for administration.[2] It is administered as a 15-minute IV infusion, every 6 hours as needed, not to exceed the maximum total daily dose of 4,000 mg acetaminophen and 1,200 mg of ibuprofen in 24 hours.[2]

- ENDS –

This product has been approved for marketing in the United States by the U.S. 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 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 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.

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INDICATIONS AND USAGE

COMBOGESIC® IV is indicated in adults (over age 18) where an intravenous route of administration is considered clinically necessary for:

- The relief of mild to moderate pain.
- The management of moderate to severe pain as an adjunct to opioid analgesics.

LIMITATIONS OF USE

COMBOGESIC® IV is indicated for short-term use of five days or less.

IMPORTANT SAFETY INFORMATION

WARNING: HEPATOTOXICITY, CARDIOVASCULAR RISK, and GASTROINTESTINAL RISK

- **RISK OF MEDICATION ERRORS: Take care when prescribing, preparing, and administering COMBOGESIC® IV to avoid dosing errors which could result in accidental overdose and death.**
- **HEPATOTOXICITY: COMBOGESIC® IV contains acetaminophen which has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most cases of liver injury are associated with doses exceeding 4,000 mg per day and often involve more than one acetaminophen-containing product.**
- **CARDIOVASCULAR RISK: COMBOGESIC® IV contains ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID). NSAIDs cause an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.**
- **COMBOGESIC® IV is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.**
- **GASTROINTESTINAL RISK: NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk.**

CONTRAINDICATIONS

COMBOGESIC® IV is contraindicated in:

- Patients with known hypersensitivity to acetaminophen, ibuprofen, other NSAIDs or to any components of this product.
- Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.
- Patients with severe hepatic impairment or severe active liver disease.

WARNINGS & PRECAUTIONS

- **Hepatotoxicity.** COMBOGESIC® IV contains acetaminophen and ibuprofen. Acetaminophen has been associated with cases of acute liver failure; the risk is higher in those with underlying liver disease and in those who ingest alcohol. Use in patients with hepatic impairment is not recommended. Elevations of ALT or AST have been reported in NSAID-treated patients.
- **Cardiovascular Thrombotic Events.** To minimize the risks of CV events, use the lowest effective dose for the shortest duration possible.
- **Gastrointestinal Bleeding, Ulceration, and Perforation.** NSAIDs may cause serious and sometimes fatal GI adverse events at any time and without warning. Avoid use in patients at higher risk. In concomitant use with low-dose aspirin, monitor patients more closely for evidence of GI bleeding.
- **Hypertension.** NSAIDs can lead to onset of new hypertension or worsening of pre-existing hypertension, which may contribute to the increased incidence of CV events.
- **Heart Failure and Edema.** Avoid use in patients with severe heart failure unless benefits outweigh risk.
- **Renal Toxicity and Hyperkalemia.** Use in patients with renal impairment is not recommended. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Increases in serum potassium concentration, including hyperkalemia, have been reported.

- **Hypersensitivity and Anaphylactic Reactions.** Hypersensitivity and anaphylaxis associated with ibuprofen and acetaminophen have been reported, including life-threatening anaphylaxis associated with acetaminophen.
- **Exacerbation of Asthma Related to Aspirin Sensitivity.** Patients with asthma may have intolerance to aspirin and other NSAIDs.
- **Serious Skin Reactions.** Acetaminophen or NSAIDs may cause serious skin reactions such as exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal and may occur without warning. Discontinue the use of COMBOGESIC® IV at the first appearance of skin rash or any other sign of hypersensitivity.
- **Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).** DRESS that may be life-threatening or fatal has been reported in patients taking NSAIDs.
- **Fetal Toxicity: Premature Closure of Fetal Ductus Arteriosus.** Avoid use of COMBOGESIC® IV in pregnant women at about 30 weeks gestation and later. COMBOGESIC® IV increases the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.
- **Oligohydramnios/Neonatal Renal Impairment.** Use of COMBOGESIC® IV at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.
- **Hematologic Toxicity.** Anemia has occurred in NSAID-treated patients and NSAID-treatment may increase the risk of bleeding events.
- **Ophthalmological Effects.** Blurred or diminished vision, scotomata, and/or changes in color vision have been reported with oral ibuprofen.
- **Aseptic Meningitis**. Aseptic meningitis with fever and coma has been observed in patients on oral ibuprofen.
- **Masking of Inflammation and Fever.** Activity of COMBOGESIC® IV in reducing inflammation, and possibly fever, may diminish signs of infections.
- **Laboratory Monitoring.** Monitor patients on NSAID treatment with a CBC and a chemistry profile as clinically indicated.

ADVERSE REACTIONS

The most common adverse reactions (≥ 3%) were infusion site pain, nausea, constipation, dizziness, infusion site extravasation, vomiting, headache, and somnolence.

DRUG INTERACTIONS

- **Drugs That Interfere with Hemostasis.** Ibuprofen and anticoagulants have a synergistic effect on bleeding. Concomitant use increases the risk of serious bleeding. Concomitant use of drugs that interfere with serotonin reuptake and an NSAID may increase the risk of bleeding.
- **ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers.** NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or Beta-Blockers. In the elderly, volume depleted, or those that have renal impairment, concomitant use with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure.
- **Diuretics.** NSAIDs can reduce the natriuretic effect of loop diuretics and thiazides in some patients.
- **Digoxin.** Concomitant use of ibuprofen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
- **Lithium.** NSAIDs produced an elevation of plasma lithium levels and a reduction in renal lithium clearance.
- **Methotrexate.** Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity.
- **Cyclosporine.** Concomitant use of NSAIDS and cyclosporine may increase cyclosporine's nephrotoxicity.
- **NSAIDS and Salicylates.** Concomitant use with other NSAIDs or salicylates increases the risk of GI toxicity.
- **Pemetrexed.** Concomitant use of NSAIDS and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity.

For more information, please see the full Prescribing Information, available at www.hikma.com.

To report an adverse event or product complaint, please contact us at us.hikma@primevigilance.com or call 1-877-845-0689 or 1-800-962-8364. Adverse events may also be reported to the FDA directly at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. Daniels SE, Playne R, Stanescu I, et al. Efficacy and safety of an intravenous acetaminophen/ibuprofen fixed-dose combination after bunionectomy: a randomized, double-blind, factorial,

placebo-controlled trial. *Clinical Therapeutics*. 2019;41(10). **2.** COMBOGESIC® IV (acetaminophen 1000 mg and ibuprofen 300 mg) [package insert]. **3.** Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of post operative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016;17:131-157.