Working to improve your health

6 February 2024

Maxigesic IV launched in the United States

AFT Pharmaceuticals (NZX: AFT, ASX: AFP) announces Maxigesic IV®, the patented intravenous form of its family of pain relief medicines, has today been launched in the US by its licensee Hikma Pharmaceuticals.

The launch of the medicine, under the brand Combogesic IV®, is the first patented, New Zealand developed medicine with clinical studies in the world's largest healthcare market. The first commercial sale of the medicine in the US is expected in the coming weeks, a milestone that will trigger a US$6 million licensee fee to AFT and its development partner Belgium's Hyloris Pharmaceuticals.

AFT expects its share of this license fee to accrue in the current financial year (estimated at around NZ$6 million).[1]

The company is currently in its usual month-end preparation and review of progress and projections for FY2024 (being for the year ending 31 March 2024) and expects to update the market on its FY2024 guidance within a fortnight once this process is completed.

"The launch of Maxigesic IV in the US, the world's largest market for pain relief[2], is a significant achievement for AFT," said AFT Co-Founder and Managing Director Dr Hartley Atkinson.

"We are delighted with the speed with which our partner Hikma, a leading supplier of injectable medicines in the US and around the world, has brought the medicine to market post-approval and the opportunity it shares with us on the potential of the medicine.

"Maxigesic IV represents a significant innovation for the management of pain. It offers effective pain relief and importantly offers clinicians an alternative to opioid analgesics.

"The launch also represents a beachhead for the commercialisation of Maxigesic in the US and potentially our broader portfolio of medicines. Our next goal is the finalization of plans to launch Maxigesic Rapid, a prescription-only tablet. We have been working on setting up AFT representation in North America in order to support commercialisation with identified partners.

[1] As previously disclosed, AFT's practice is to exclude the benefit of one-off milestone payments of this nature in guidance.

[2] https://www.mordorintelligence.com/industry-reports/pain-management-market

Hikma President of Injectables Dr Bill Larkins said: "The approval of Combogesic® IV is an important step in providing hospitals and health care providers in the US with an alternative treatment option for managing patients' pain.

"This is another example of how we continue to expand our portfolio of critical medicines and we are pleased to make this important new treatment option available for patients, helping to put better health within reach, every day."

Hikma's announcement of the launch of Maxigesic IV is attached to this announcement.

Maxigesic IV is licensed in over 100 countries and marketed in over 20. It offers a unique combination of 1,000 mg of acetaminophen (paracetamol) and 300 mg of ibuprofen. This combination of medicines with different mechanisms of action in a single formulation provides:

- Shorter onset to analgesia[3]
- Superior analgesia efficacy and comparable safety in common adverse events[2]
- Sustained pain-management results[2]

In a Phase 3 clinical trial, Maxigesic IV provided more than double the pain relief than that of acetaminophen (paracetamol) IV or ibuprofen IV alone.[2] Time to meaningful pain relief was shorter in the Maxigesic IV group than that in the Ibuprofen IV or placebo groups. Maxigesic IV also allowed for superior analgesia efficacy.[2]

For and on behalf of AFT Pharmaceuticals Limited by Malcolm Tubby, Chief Financial Officer.

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About AFT Pharmaceuticals

AFT is a growing multinational pharmaceutical company that develops, markets, and distributes a broad portfolio of pharmaceutical products across a wide range of therapeutic categories which are distributed across all major pharmaceutical distribution channels: over the counter (OTC), prescription and hospital. Our product portfolio comprises both proprietary and in-licensed products, and includes patented, branded, and generic drugs[4]. Our business model is to develop and in-license products for sale by our own dedicated sales teams in our home markets of Australia and New Zealand and in certain Southeast Asian markets, and to out-license our products to local licensees and distributors to over 125 countries around the world. For more information about the company, visit our website www.aftpharm.com.

[3] Daniels SE, Playne R, Stanescu I, Zhang J, Gottlieb IJ, Atkinson HC. 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).

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Press Release

Hikma announces US launch of COMBOGESIC® IV

Offers health care providers a new multimodal approach to adult pain management

London, 5 February 2024 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces the launch of COMBOGESIC® IV (acetaminophen and ibuprofen) injection in the US.

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). It was approved by the US FDA in October 2023 for use in adults where an intravenous route of administration is considered clinically necessary for: (i) the relief of mild to moderate pain; and (ii) the management of moderate to severe pain as an adjunct to opioid analgesics.[1]

The American Society of Anesthesiology's (ASA) evidence-based recommendations emphasize the importance of a multimodal approach to pain management using multiple interventions with different mechanisms of action that may offer additive or synergistic effects to optimize pain relief.[2]

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

- Shorter onset to analgesia[3]
- Superior analgesia efficacy and comparable safety in common adverse events[3]
- Sustained pain-management results[3]

In a Phase 3 clinical trial, COMBOGESIC® IV provided more than double the pain relief than that of acetaminophen IV and ibuprofen IV alone.[3] Time to meaningful pain relief was shorter in the COMBOGESIC® IV group than that in the Ibuprofen IV or placebo groups.[3] COMBOGESIC® IV also allows for superior analgesia efficacy.[3]

"The approval of COMBOGESIC® IV is an important step in providing hospitals and health care providers in the US with an alternative treatment option for managing patients' pain," said Dr. Bill Larkins, President of Injectables, Hikma. "This is another example of how we continue to expand our portfolio of critical medicines and we are pleased to make this important new treatment option available for patients, helping to put better health within reach, every day."

In 2021, Hikma signed an exclusive license and distribution agreement with AFT Pharmaceuticals (AFT) for the commercialization of COMBOGESIC® IV in the US. Under the trade name of MAXIGESIC® IV outside of the United States, COMBOGESIC® IV is licensed in over 100 countries and marketed in over 20 countries.

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.[1] It offers health care providers a new 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

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[1] COMBOGESIC® IV (acetaminophen 1000 mg and ibuprofen 300 mg) [package insert].

[2] 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.

[3] Daniels SE, Playne R, Stanescu I, Zhang J, Gottlieb IJ, Atkinson HC. 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).

required for administration.[1] 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.[1]

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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 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 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 8,800 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

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.

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. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with doses of acetaminophen that exceed 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 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 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.**

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CONTRAINDICATIONS

COMBOGESIC® IV is contraindicated in:

- Patients with previous demonstrated hypersensitivity to acetaminophen, ibuprofen, other NSAIDs or to any of the excipients/components of this product.
- Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
- The treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Patients with severe hepatic impairment or severe active liver disease.

WARNINGS & PRECAUTIONS

- **Risk of Medication Errors.** Take care when prescribing, preparing, and administering COMBOGESIC® IV in order to avoid dosing errors which could result in accidental overdose and death. In particular, be careful to ensure that the dose in milligrams (mg) and milliliters (mL) is not confused, the dosing is based on weight for patients under 50 kg, infusion pumps are properly programmed, and the total daily dose of acetaminophen from all sources does not exceed maximum daily limits.
- **Hepatotoxicity. (i)** COMBOGESIC® IV contains acetaminophen which has been associated with cases of acute liver failure, at times resulting in liver transplant and death. The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen. The use of COMBOGESIC® IV in patients with hepatic impairment is not recommended. **(ii)** COMBOGESIC® IV contains ibuprofen. Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs.
- **Cardiovascular Thrombotic Events.** Trials suggest that NSAIDs, taken for up to 3 years, elevate the risk of serious cardiovascular events like myocardial infarction and stroke. To minimize these risks, the lowest effective dose for the shortest duration possible should be used in these patients.
- **Gastrointestinal Bleeding, Ulceration, and Perforation.** NSAIDs cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small or large intestine, which can be fatal. These adverse events can occur at any time, with or without warning symptoms. Avoid use in patients at higher risk. In concomitant use with low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding.
- **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. These serious events may occur without warning. Inform patients about the signs and symptoms and discontinue the use of the drug at the first appearance of skin rash or any other sign of hypersensitivity. COMBOGESIC® IV is contraindicated in patients with previous serious skin reactions to acetaminophen or NSAIDs.
- **Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as COMBOGESIC® IV. Some of these events have been fatal or life-threatening.
- **Hypersensitivity and Anaphylactic Reactions.** There have been post marketing reports of hypersensitivity and anaphylaxis, including life-threatening anaphylaxis associated with the use of acetaminophen.
- **Hypertension.** NSAIDs can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events.
- **Heart Failure and Edema.** Studies have demonstrated an increase in hospitalizations for heart failure in NSAID-treated patients compared to placebo-treated patients. Additionally, in a study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death. Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ibuprofen may blunt the CV effects of several therapeutic agents used to treat these medical conditions.
- **Renal Toxicity and Hyperkalemia.** Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. No information is available regarding the use of COMBOGESIC® IV in patients with advanced renal disease.
- **Exacerbation of Asthma Related to Aspirin Sensitivity.** Patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe bronchospasm, which can be fatal and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, COMBOGESIC® IV is contraindicated in

patients with this form of aspirin sensitivity.

- **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.
- **Fetal Toxicity: 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. This may be due to occult or gross GI blood loss, fluid retention, or an incompletely described effect on erythropoiesis. NSAIDs included in COMBOGESIC® IV may increase the risk of bleeding events.
- **Masking of Inflammation and Fever.** Activity of COMBOGESIC® IV in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.
- **Ophthalmological Effects.** If a patient develops ophthalmological complaints while receiving COMBOGESIC® IV, the drug should be discontinued, and the patient should have an ophthalmologic examination.
- **Increased Risk of Hepatotoxicity with Concomitant Use of Other Acetaminophen-containing Products.** COMBOGESIC® IV should not be used concomitantly with other acetaminophen containing products.
- **Use with Alcohol.** COMBOGESIC® IV should not be used concomitantly with alcoholic beverages.
- **Laboratory Monitoring.** Consider monitoring patients on NSAID treatment with a CBC and a chemistry profile as clinically indicated.

ADVERSE REACTIONS

The most common TEAEs (occurring in ≥ 3% of COMBOGESIC® IV -treated participants) were related to the infusion site (infusion site pain, infusion site extravasation), or affected the gastrointestinal (nausea, vomiting, constipation) or nervous (dizziness, headache, somnolence) systems. Other skin and subcutaneous-related TEAEs (pruritis, hyperhidrosis) also affected around 2 to 3% of the study population, as did procedural nausea and polyuria.

DRUG INTERACTIONS

A number of known or potential interactions between COMBOGESIC® IV and other drugs/drug classes exist. Please refer to the Drug Interactions in the Prescribing Information for further information.

- **Drugs That Interfere with Hemostasis.** Ibuprofen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of ibuprofen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. Concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
- **Aspirin.** There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID increases the risk of serious gastrointestinal (GI) events.
- **ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers.** NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or Beta-Blockers.
- **Diuretics.** NSAIDs can reduce the natriuretic effect of loop diuretics and thiazides in some patients.
- **Lithium.** NSAIDs produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Monitor patients for signs of lithium toxicity.
- **Methotrexate.** Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). Monitor patients for methotrexate toxicity.

USE IN SPECIFIC POPULATIONS

- **Females and Males of Reproductive Potential.** Use of acetaminophen may cause reduced fertility in males and females of reproductive potential. It is not known whether these effects on fertility are reversible. The use of NSAIDs may delay or prevent rupture of ovarian follicles. Consider withdrawal of NSAID-containing products in women who have difficulties conceiving or who are undergoing investigation of infertility.
- **Geriatric Use.** Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Elderly patients (65 years and older) are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects.
- **Hepatic Impairment.** Use of COMBOGESIC® IV in patients with hepatic impairment is not recommended.
- **Renal Impairment.** The use of COMBOGESIC® IV in these patients is not recommended as it may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

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.

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 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.

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