ICU MANAGEMENT & PRACTICE

The Medicines Company To Present Data on Innovative Surgical Anesthetic at ANESTHESIOLOGY 2015

- *Investigational compound ABP-700 abstract awarded "Best of Show" from International Society of Anesthetic Pharmacology (ISAP) in advance of ANESTHESIOLOGY 2015*
- *Follows on recent FDA approval of IONSYS® (fentanyl iontophoretic transdermal system) CII for moderate to severe postoperative pain*

The Medicines Company will present new clinical data on ABP-700 – a novel intravenous (IV) anesthetic under development for general anesthesia and procedural sedation – at ANESTHESIOLOGY 2015, the annual congress of the American Society of Anesthesiologists, October 24-28 in San Diego. ABP-700 has the potential to advance the safety and efficiency of surgical and procedural care.

More than 315 million surgeries are performed worldwide each year [1], yet there have been few innovations in anesthetics since the introduction of propofol in 1987. "Innovations in anesthesia have not kept pace with overall demand for surgery or the shift to less invasive, out-patient procedures requiring fast-acting and quickly reversible agents with improved safety profiles," said Clive A. Meanwell, MD, PhD, Chief Executive Officer of The Medicines Company. "We are encouraged by promising early results with ABP-700 demonstrating the dramatic potential of this compound to address shortcomings of currently available drugs including propofol."

In a related announcement, the Company announced that the abstract "Safety, Pharmacokinetics and Pharmacodynamics of ABP-700: A Novel Intravenous Anesthetic" has been awarded "Best in Show" at the annual meeting of the International Society for Anaesthetic Pharmacology (ISAP) to be held on October 23, also in San Diego.

ABP-700 is one of three agents in The Medicines Company portfolio of surgical and perioperative products that will have a presence at ANESTHESIOLOGY 2015. IONSYS® (fentanyl iontophoretic transdermal system) is the first needle-free, patient-controlled, pre-programmed fentanyl delivery system, for the short-term management of acute post-operative pain in adult patients requiring opioid analgesia in the hospital.

As with anesthesia challenges, innovation in post-surgical pain management has lagged behind rapidly expanding need. Approximately 75 percent of surgical patients experience post-operative pain, a figure that has not changed since the 1990s. [2]

IONSYS, approved by the Food and Drug Administration (FDA) in April 2015, is effective in managing pain as compared to IV-PCA morphine while allowing patients mobility during recovery compared to the limitations of needle-based intravenous patient-controlled analgesia (IV-PCA). As a result, patients may be better able to participate in physical therapy and potentially free hospital staff from managing complex pumps and lines so that time and resources can be better focused on actual patient care.

In addition to ABP-700 and IONSYS, CLEVIPREX® (clevidipine) injectable emulsion will also be featured as part of the Company's overall surgical and perioperative portfolio. CLEVIPREX is a fast-acting, selective calcium channel blocker indicated for reduction of blood pressure when oral therapy is not feasible or desirable.

Details for the oral presentation and poster for ABP-700 are summarized below:

Conference Call

ABP-700 results will be discussed on a telephone and WebEx conference call on October 27th at 5:30 am PDT (8:30 am EDT). The following experts will be participating on the call:

- J. Robert Sneyd, Dean and Professor of Anesthesia, Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK
- Michel Struys, Professor and Chairman, Department of Anesthesiology, University Medical Center Groningen, Netherlands
- Talmage Egan, MD, Chairman, Department of Anesthesiology, University of Utah Health Care
- Doug Raines, MD, Professor of Anesthesia, Massachusetts General Hospital and Harvard Medical School, and inventor of ABP-700

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This call is being webcast and can be accessed via The Medicines Company website at www.themedicinescompany.com.

In addition, the slides that will be used during the call can be found on the event page of the Investor Relations section of our website www.themedicinescompany.com.

About ABP-700

ABP-700, an investigational product not approved for commercial use in any market, is a novel, positive allosteric modulator of the GABAA receptor currently being developed for general anesthesia and procedural sedation. ABP-700 is from a family of compounds invented by Dr. Douglas Raines at the Massachusetts General Hospital, all based on existing anesthetics which are variants of etomidate.

About IONSYS® (fentanyl iontophoretic transdermal system), CII

IONSYS® (fentanyl iontophoretic transdermal system) CII, contains fentanyl, an opioid agonist. IONSYS is indicated for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia in the hospital.

Limitations of Use:

- Only for use in patients who are alert enough and have adequate cognitive ability to understand the directions for use.
- Not for home use. IONSYS is for use only in patients in the hospital. Discontinue treatment with IONSYS before patients leave the hospital.
- IONSYS is for use after patients have been titrated to an acceptable level of analgesia using alternate opioid analgesics.

IMPORTANT SAFETY INFORMATION

WARNING: HOSPITAL USE ONLY; LIFE-THREATENING RESPIRATORY DEPRESSION; IONSYS REMS; ADDICTION, ABUSE, AND MISUSE; and CYTOCHROME P450 3A4 INTERACTION

Life Threatening Respiratory Depression

Use of IONSYS may result in potentially life-threatening respiratory depression and death as a result of the active drug, fentanyl. Only the patient should activate IONSYS dosing.

Accidental exposure to an intact IONSYS or to the hydrogel component, especially by children, through contact with skin or contact with mucous membranes, can result in a fatal overdose of fentanyl.

IONSYS is for use only in patients in the hospital. Discontinue treatment with IONSYS before patients leave the hospital.

IONSYS Risk Evaluation and Mitigation Strategy (REMS) Program

- Because of the potentially life-threatening respiratory depression resulting from accidental exposure, IONSYS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the IONSYS REMS Program.

Addiction, Abuse, and Misuse

- IONSYS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors or conditions.

Cytochrome P450 3A4 Interaction

The concomitant use of IONSYS with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving IONSYS and any CYP3A4 inhibitor or inducer.

Contraindications

- Significant respiratory depression
- Acute or severe bronchial asthma
- Known or suspected paralytic ileus and GI obstruction
- Hypersensitivity to fentanyl, cetylpyridinium chloride (e.g., Cepacol®), or any components of IONSYS

Warnings and Precautions

- Interactions with CNS depressants: Hypotension, profound sedation, coma, respiratory depression, and death may result if IONSYS is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). Monitor patients closely if co-administration is required.
- Risk of Injury During MRI: IONSYS contains metal parts and must be removed and properly disposed of before a Magnetic Resonance Imaging (MRI) procedure. Monitor any patients wearing IONSYS with inadvertent exposure to an MRI for signs of central nervous system and respiratory depression.
- Risk of IONSYS Use During Other Procedures or Near Certain Equipment: Use of IONSYS during cardioversion, defibrillation, X-ray, CT, or diathermy can damage IONSYS and should be removed and properly disposed of before these procedures. Avoid contact with synthetic materials (such as carpeted flooring) to reduce the possibility of electrostatic discharge and damage to IONSYS. Avoid exposing IONSYS to electronic security systems to reduce the possibility of damage to IONSYS. Use of IONSYS near communications equipment (e.g., base stations for radio telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast radio) and Radio Frequency Identification (RFID) transmitters can damage IONSYS. If exposure to the above procedures, electronic security systems, electrostatic discharge, communications equipment, or RFID transmitters occurs, and if IONSYS does not appear to function normally, remove IONSYS and replace with a new IONSYS.
- Topical Skin Reactions: Topical skin reactions may occur with use of IONSYS and are typically limited to the site application area. If a severe skin reaction is observed, remove IONSYS and discontinue further use.
- Use in Elderly, Cachectic, and Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients. Monitor such patients closely especially when IONSYS is used concomitantly with other drugs that depress respiration.
- Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory

depression for respiratory depression, particularly when initiating therapy with IONSYS. Consider the use of alternative non-opioid analgesics in these patients if possible.

- Hypotensive Effect: IONSYS may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients after initiating IONSYS. Avoid the use of IONSYS in patients with circulatory shock as IONSYS may cause vasodilation that can further reduce cardiac output and blood pressure.
- Patients with Head Injury or Increased Intracranial Pressure: IONSYS is not suitable for use in patients who are not alert and able to follow directions. Monitor patients using IONSYS who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with IONSYS. Avoid use of IONSYS in patients with impaired consciousness or coma. IONSYS may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Opioids may obscure the clinical course of patients with head injury.
- Use in Patients with Gastrointestinal Conditions: IONSYS is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. Fentanyl may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms. Opioids may cause increases in serum amylase.
- Use in Patients with Convulsive or Seizure Disorders: IONSYS may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during IONSYS therapy.
- Bradycardia: IONSYS may produce bradycardia in some patients. Monitor patients with bradyarrhythmias closely for changes in heart rate, particularly when initiating therapy with IONSYS.
- Hepatic Impairment: Insufficient data are available on the use of IONSYS in patients with impaired hepatic function. Monitor for signs of sedation and respiratory depression in patients with hepatic impairment.
- Renal Impairment: A clinical pharmacology study with intravenous fentanyl in patients undergoing kidney transplantation has shown that patients with high blood urea nitrogen level had low fentanyl clearance. Monitor for signs of sedation and respiratory depression in patients with renal impairment.

Adverse Reactions

Most common (frequency ≥2%) headache, hypotension, nausea, vomiting, anemia, dizziness, application site reaction-erythema, pruritus, and urinary retention.

About CLEVIPREX® (clevipidine) Injectable Emulsion

CLEVIPREX® (clevidipine) Injectable Emulsion is a dihydropyridine calcium channel blocker indicated for the reduction of blood pressure when oral therapy is not feasible or not desirable.

Important Safety Information

CLEVIPREX® (clevidipine) Injectable Emulsion is contraindicated in patients with:

- Allergies to soybeans, soy products, eggs, or egg products;
- Defective lipid metabolism seen in conditions such as pathologic hyperlipemia, lipoid nephrosis, or acute pancreatitis if it is accompanied by hyperlipidemia; and
- Severe aortic stenosis.

CLEVIPREX® is intended for intravenous use. Use aseptic technique and discard any unused product within 12 hours of stopper puncture.

Hypotension and reflex tachycardia are potential consequences of rapid upward titration of CLEVIPREX®. If either occurs, decrease the dose of CLEVIPREX®. There is limited experience with short-duration therapy with beta-blockers as a treatment for CLEVIPREX® -induced tachycardia. Beta-blocker use for this purpose is not recommended.

CLEVIPREX® contains approximately 0.2 g of lipid per mL (2.0 kcal). Lipid intake restrictions may be necessary for patients with significant disorders of lipid metabolism.

Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure. Monitor heart failure patients carefully.

CLEVIPREX® is not a beta-blocker, does not reduce heart rate, and gives no protection against the effects of abrupt beta-blocker withdrawal. Beta-blockers should be withdrawn only after a gradual reduction in dose.

Patients who receive prolonged CLEVIPREX® infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped.

There is no information to guide use of CLEVIPREX® in treating hypertension associated with pheochromocytoma.

Most common adverse reactions for CLEVIPREX® (>2%) are headache, nausea, and vomiting.

Source & Image Credit: The Medicine Company

1 Lancet, Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development; Mera et al; April 2015.

2 Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014;30(1):149-160

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