SUBLOCADE® Long-Term Safety Data
Published in *Journal of Clinical Psychopharmacology*

Slough, UK and Richmond, VA, April 16, 2020 – Indivior PLC (LON: INDV) today announced the publication of long-term safety data for SUBLOCADE® (buprenorphine extended-release) injection, for subcutaneous use (CIII).

The manuscript entitled "*Treating Opioid Use Disorder with a Monthly Subcutaneous Buprenorphine Depot Injection: 12-month Safety, Tolerability and Efficacy Analysis*" was published online on April 9, 2020 and will appear in an upcoming print issue of the *Journal of Clinical Psychopharmacology*.[1]

This open-label multicenter study (NCT 02510014) in adults with moderate or severe opioid use disorder (OUD) enrolled 257 participants from a previously conducted placebo-controlled, double-blind Phase III trial (*Rollover* group) and 412 *De Novo* participants not previously treated with SUBLOCADE. By study end, 60.7% participants completed the study and received up to 12 injections. The main findings were as follows:

- The safety profile of up to 12-month SUBLOCADE treatment was consistent with that of transmucosal buprenorphine, with the exception of the anticipated injection-site reactions.[1]
- Overall, 66.8% of participants reported >1 treatment-emergent adverse event (TEAE). Injection-site TEAEs (13.2% of participants), were mostly mild or moderate in severity.
- An integrated analysis of the double-blind and open-label study participants showed that the incidence of TEAEs, including injection-site TEAEs, were lower in the second 6 months of treatment versus the first 6 months.
- There were no unexpected safety signals detected and no TEAEs potentially related to respiratory depression.
- The hepatic safety profile of SUBLOCADE was comparable to that reported for transmucosal buprenorphine and longer exposure to the highest 300 mg maintenance dose of SUBLOCADE did not worsen hepatic laboratory assessments. There were no cases of hepatocellular injury indicated by increased AST/ALT with jaundice and no removal of SUBLOCADE was required.

- Efficacy was evaluated using Urine Drug Screen for opioids plus self-reported illicit opioid use combined into a single endpoint. After 12 months of SUBLOCADE treatment, 61.5% of the *Rollover* participants and 75.8% of the *De Novo* participants were free of illicit opioid use.

"Recent research has shown that treatment is most helpful when it addresses opioid use disorder as a chronic disease that requires services and support structures over an extended period of time," said Christian Heidbreder, PhD, Indivior's Chief Scientific Officer. "Data from this open-label study provide additional scientific evidence in support of the long-term safety profile of SUBLOCADE and may help clinicians to determine how best they can help patients achieve and maintain recovery."

ABOUT SUBLOCADE[2]

INDICATION AND USAGE

SUBLOCADE® (buprenorphine extended-release) injection, for subcutaneous use (CIII) is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product followed by a dose adjustment period for a minimum of seven days.

SUBLOCADE should be used as part of a complete treatment program that includes counseling and psychosocial support.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY

- **Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously.**
- **Because of the risk of serious harm or death that could result from intravenous self-administration, SUBLOCADE is only available through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified in this program and comply with the REMS requirements.**

Prescription use of this product is limited under the Drug Addiction Treatment Act.

SUBLOCADE should only be prepared and administered by a healthcare provider.

CONTRAINDICATIONS

SUBLOCADE should not be administered to patients who have been shown to be hypersensitive to buprenorphine or any component of the ATRIGEL® delivery system.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse: SUBLOCADE contains buprenorphine, a Schedule III controlled substance that can be abused in a manner similar to other opioids. Buprenorphine is sought by people with opioid use disorder and is subject to criminal diversion. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors.

Risk of Life-Threatening Respiratory Depression and Concomitant Use of Benzodiazepines or Other CNS Depressants with Buprenorphine: Buprenorphine has been associated with life-threatening respiratory depression, overdose, and death, particularly when misused by self-injection or with concomitant use of benzodiazepines or other CNS depressants, including alcohol. Warn patients of the potential danger of self-administration of benzodiazepines, other CNS depressants, opioid analgesics, and alcohol while under treatment with SUBLOCADE. Counsel patients that such medications should not be used concomitantly unless supervised by a healthcare provider.

Use with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

Opioids can cause sleep-related breathing disorders; e.g., central sleep apnea (CSA), sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. Consider decreasing the opioid using best practices for opioid taper if CSA occurs.

Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy. NOWS may be life-threatening if not recognized and treated in the neonate. Newborns should be observed for signs of NOWS and managed accordingly. Advise pregnant women receiving opioid addiction treatment with SUBLOCADE of the risk of neonatal opioid withdrawal syndrome.

Adrenal Insufficiency: Adrenal insufficiency has been reported with opioid use. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off the opioid.

Discontinuation of SUBLOCADE Treatment: Due to the long-acting nature of SUBLOCADE, if treatment is discontinued, monitor patients for several months for withdrawal and treat appropriately.

Inform patients that they may have detectable levels of buprenorphine for a prolonged period of time after treatment with SUBLOCADE. Considerations of drug-drug interactions, buprenorphine effects, and analgesia may continue to be relevant for several months after the last injection.

Risk of Hepatitis, Hepatic Events: Because cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine, monitor liver function tests prior to treatment and monthly during treatment.

Hypersensitivity Reactions: Hypersensitivity to buprenorphine-containing products have been reported most commonly as rashes, hives, and pruritus. Some cases of bronchospasm, angioneurotic edema, and anaphylactic shock have also been reported.

Precipitation of Opioid Withdrawal in Patients Dependent on Full Agonist Opioids: Buprenorphine may precipitate opioid withdrawal signs and symptoms in persons who are currently physically dependent on full opioid agonists such as heroin, morphine, or methadone before the effects of the full opioid agonist have subsided. Verify that patients have tolerated and are dose adjusted on transmucosal buprenorphine before subcutaneously injecting SUBLOCADE.

Risks Associated With Treatment of Emergent Acute Pain: When patients need acute pain management, or may require anesthesia, treat patients receiving SUBLOCADE currently or within the last 6 months with a non-opioid analgesic whenever possible. If opioid therapy is required, patients may be treated with a high-affinity full opioid analgesic under the supervision of a physician, with particular attention to respiratory function, as higher doses may be required for analgesic effect and therefore, a higher potential for toxicity exists with opioid administration.

Advise patients of the importance of instructing their family members, in the event of emergency, to inform the treating healthcare provider or emergency room staff that the patient is physically dependent on an opioid and that the patient is being treated with SUBLOCADE.

Use in Opioid Naïve Patients: Because death has been reported for opioid naïve individuals who received buprenorphine sublingual tablet, SUBLOCADE is not appropriate for use in opioid naïve patients.

Use in Patients With Impaired Hepatic Function: Because buprenorphine levels cannot be rapidly decreased, SUBLOCADE is not recommended for patients with pre-existing moderate to severe hepatic impairment. Patients who develop moderate to severe hepatic impairment while being treated with SUBLOCADE should be monitored for several months for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Use in Patients at Risk for Arrhythmia: Buprenorphine has been observed to prolong the QTc interval in some patients participating in clinical trials. Avoid use of buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval.

Impairment of Ability to Drive or Operate Machinery: SUBLOCADE may impair the mental or physical abilities required for the performance of potentially dangerous

tasks such as driving a car or operating machinery. Caution patients about driving or operating hazardous machinery until they are reasonably certain that SUBLOCADE does not adversely affect their ability to engage in such activities.

Orthostatic Hypotension: Buprenorphine may produce orthostatic hypotension.

Elevation of Cerebrospinal Fluid Pressure: Buprenorphine may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Elevation of Intracholedochal Pressure: Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

Effects in Acute Abdominal Conditions: Buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Unintentional Pediatric Exposure: Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it.

ADVERSE REACTIONS: Adverse reactions commonly associated with SUBLOCADE (≥5% of subjects) during clinical trials were constipation, headache, nausea, vomiting, increased hepatic enzymes, fatigue, and injection site pain and pruritus. This is not a complete list of potential adverse events. Please see the full Prescribing Information for a complete list.

DRUG INTERACTIONS
CYP3A4 Inhibitors and Inducers: Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over- or under-dosing.

Serotonergic Drugs: If concomitant use with serotonergic drugs is warranted, monitor for serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug.

Consult the full Prescribing Information for SUBLOCADE for more information on potentially significant drug interactions.

USE IN SPECIFIC POPULATIONS
Pregnancy: Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.

Lactation: Buprenorphine passes into the mother’s milk. Advise breastfeeding women to monitor the infant for increased drowsiness and breathing difficulties.

Fertility: Chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible.

Geriatric Patients: Monitor geriatric patients receiving SUBLOCADE for sedation or respiratory depression.

To report pregnancy or side effects associated with taking SUBLOCADE, please call 1-877-782-6966.

For more information about SUBLOCADE, see the full Prescribing Information including BOXED WARNING, and Medication Guide. For REMS information visit www.sublocadeREMS.com.

About Opioid Use Disorder (OUD)

Opioid addiction isn't a moral weakness. Opioid addiction is a chronic disease called Opioid Use Disorder (OUD)[3] in which people develop a pattern of using opioids that can lead to negative consequences.[4] Opioid addiction may affect the parts of the brain that control impulses, judgment, and decision-making.[4,5] Patients become trapped in a cycle of opioid use, which produces changes in brain function that can reduce their ability to control their use.[4,6]

In 2018, an estimated 10.3 million people aged 12 or older misused opioids in the past year, including 9.9 million prescription pain reliever misusers and 808,000 heroin users. Approximately 506,000 people misused prescription pain relievers and used heroin in the past year.[7] SUBLOCADE is not indicated for use in children younger than 18 years of age. Buprenorphine, the active ingredient of SUBLOCADE can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it.[2]

About Indivior

Indivior is a global pharmaceutical company working to help change patients' lives by developing medicines to treat addiction and serious mental illnesses. Our vision is that all patients around the world will have access to evidence-based treatment for the chronic conditions and co-occurring disorders of addiction. Indivior is dedicated to transforming addiction from a global human crisis to a recognized and treated chronic disease.

Building on its global portfolio of opioid dependence treatments, Indivior has a pipeline of product candidates designed to both expand on its heritage in this category and potentially address other chronic conditions and co-occurring disorders of addiction, including alcohol use disorder. Headquartered in the United States in Richmond, VA, Indivior employs more than 800 individuals globally and its portfolio of products is available in over 40 countries worldwide. Visit www.indivior.com to learn more. Connect with Indivior on LinkedIn by visiting www.linkedin.com/company/indivior.

Forward-Looking Statements

This announcement contains certain statements that are forward-looking. By their nature, forward-looking statements involve risks and uncertainties as they relate to events or circumstances that may or may not occur in the future. Actual results may differ materially

from those expressed or implied in such statements because they relate to future events. Forward-looking statements include, among other things, statements regarding the Indivior Group's financial guidance for 2020 and its medium- and long-term growth outlook, its operational goals, its product development pipeline and statements regarding ongoing litigation and other statements containing the words "subject to", "believe", "anticipate", "plan", "expect", "intend", "estimate", "project", "may", "will", "should", "would", "could", "can", the negatives thereof, variations thereon and similar expressions.

Various factors may cause differences between Indivior's expectations and actual results, including, among others (including those described in the risk factors described in the most recent Indivior PLC Annual Report and in subsequent releases): factors affecting sales of Indivior Group's products and financial position; the outcome of research and development activities; decisions by regulatory authorities regarding the Indivior Group's drug applications or authorizations; the speed with which regulatory authorizations, pricing approvals and product launches may be achieved, if at all; the outcome of post-approval clinical trials; competitive developments; difficulties or delays in manufacturing and in the supply chain; disruptions in or failure of information technology systems; the impact of existing and future legislation and regulatory provisions on product exclusivity; trends toward managed care and healthcare cost containment; legislation or regulatory action affecting pharmaceutical product pricing, reimbursement or access; challenges in the commercial execution; claims and concerns that may arise regarding the safety or efficacy of the Indivior Group's products and product candidates; risks related to legal proceedings, including the indictment by the U.S. Department of Justice, potential exclusion from participating in U.S. Federal Health Care Programs; the ongoing investigative and antitrust litigation matters; the opioid national multi-district litigation and securities class action litigation; the Indivior Group's ability to protect its patents and other intellectual property; the outcome of patent infringement litigation relating to Indivior Group's products, including the ongoing ANDA lawsuits; changes in governmental laws and regulations; issues related to the outsourcing of certain operational and staff functions to third parties; uncertainties related to general economic, political, business, industry, regulatory and market conditions; and the impact of acquisitions, divestitures, restructurings, internal reorganizations, product recalls and withdrawals and other unusual items.

Consequently, forward-looking statements speak only as of the date that they are made and should be regarded solely as our current plans, estimates and beliefs. You should not place undue reliance on forward-looking statements. We cannot guarantee future results, events, levels of activity, performance or achievements. Except as required by law, we do not undertake and specifically decline any obligation to update, republish or revise forward-looking statements to reflect future events or circumstances or to reflect the occurrences of unanticipated events.

Media Contacts

US
IndiviorMediaContacts@indivior.com
+1 804-594-0836 3

UK
Tulchan Communications
+44 207-353-4200

Investor Contact
Jason Thompson
Indivior Vice President, Investor Relations
+1 804-379-1033
Jason.Thompson@indivior.com

References

1. Andorn, AC, Haight, BR, Shinde, S, Fudala, PJ, Zhao Y, Heidbreder, C, Learned, SM, Fox, NL, Nadipelli, VR, Hassman, D, Rutrick, D. Treating Opioid Use Disorder with a Monthly Subcutaneous Buprenorphine Depot Injection: 12-month Safety, Tolerability and Efficacy Analysis. *Journal of Clinical Psychopharmacology*. https://journals.lww.com/psychopharmacology/Abstract/publishahead/Treating_Opioid_Use_Disorder_With_a_Monthly.98443.aspx

2. SUBLOCADE® [Prescribing Information]. Indivior Inc., North Chesterfield, VA. October 2019.

3. U.S. Department of Health and Human Services (HHS), Office of the Surgeon General. *Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health.* Washington, DC: HHS, November 2016.

4. U.S. Department of Health and Human (HHS), Services Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment (SAMHSA). *Medication-Assisted Treatment for Opioid Addiction*. HHS Publication No. (SMA) 09-4443, First printed 2009. Revised 2011.

5. U.S. Department of Health and Human Services (HHS), National Institute on Drug Abuse, National Institutes of Health. *Drugs, Brains, and Behavior: The Science of Addiction.* HHS Publication No. (SMA) 18-5063PT5, Printed 2018.

6. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. *N Engl J Med.* 2016; 374:363-371.

7. Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health*. HHS Publication No. PEP19-5068, NSDUH Series H-54. Rockville, MD: Center for Behavioural Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/. Accessed on November 7, 2019.

###