



Indivior Inc.  
www.indivior.com

## Driving innovation in addiction medicine

Indivior is investing in research and development to pioneer life-transforming treatments in addiction medicine, and in partnerships worldwide to realize its vision that all patients will have access to quality treatment for the chronic relapsing conditions and co-occurring disorders of addiction.

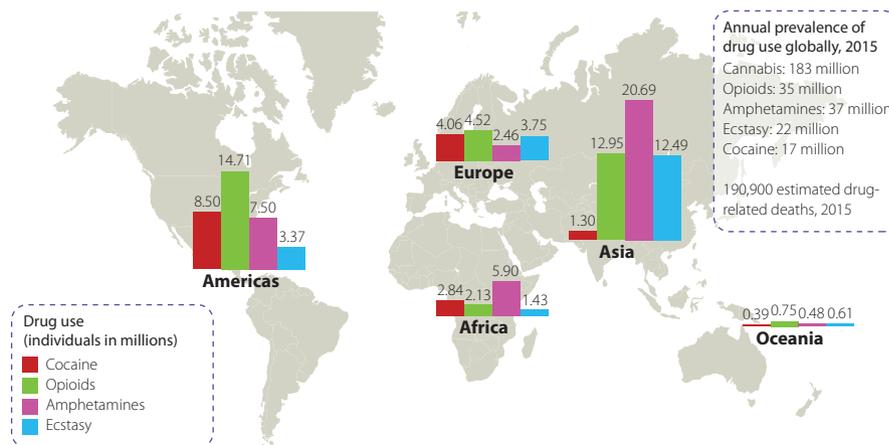
Indivior Inc., a global specialty pharmaceutical company with a 20-year legacy of leadership in patient advocacy and health policy, has built a global portfolio of treatments for opioid use disorder (OUD) and a pipeline of product candidates to address other chronic conditions and co-occurring disorders of addiction, including alcohol use disorder (AUD) and schizophrenia. All along, the company has also invested in education programs on evidence-based treatment models that have helped revolutionize modern addiction treatment. Indivior's goal is to transform the perception of addiction from a global human crisis to a chronic disease that should be recognized and treated.

The year 2017 marks 20 years since the publication of the first World Drug Report to raise international awareness of the scale of drug use globally<sup>1</sup>. In 2015, 255 million people, or approximately 5% of the global adult population aged 15–64 years, used illicit drugs at least once (Fig. 1). Of these, 29.5 million people, or 0.6% of the global adult population, were engaged in high-risk consumption of drugs. In 2015 alone, the harm caused by drug use translated into an estimated 28 million years of healthy life lost worldwide as a result of premature death and disability.

Opioids (opiates and prescription opioids) were the most harmful drugs in this context, accounting for 12 million disability-adjusted life years (DALYs), or 70% of the negative health impact associated with drug use disorders (DUDs) worldwide. In the United States alone, the misuse of opioids, together with a significant increase in heroin and fentanyl use, accounted

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**Figure 1: Global prevalence of drug use by region.** Consumption of cannabis, cocaine, opioids (opiates and prescription opioids), amphetamines and prescription stimulants, and ecstasy is at an all-time high according to the United Nations Office on Drugs and Crime<sup>1</sup>.

for approximately 25% of the estimated number of drug-related deaths in 2015. Overdose deaths in the United States were mostly driven by opioids and increased in number from 16,849 to 52,404 annually during the 1999–2015 period.

Despite this state of affairs, access to treatment of DUDs and related conditions remains limited, and currently fewer than one in six persons with DUDs receives treatment.

According to Christian Heidebreder, CSO of Indivior, “approximately 200,000 premature deaths worldwide can be attributed to the use and misuse of opioids. This figure clearly shows the rapidly evolving public health crisis that requires pioneering scientific solutions. Indivior's research and development is totally dedicated to the development of innovative therapeutics that move the international community one step closer to new treatment options that help patients with DUDs worldwide improve their quality of life and well-being.”

### Addressing the drug use disorder challenge

Indivior's core guiding principle—focus on patient needs to drive decisions—incites research and development (R&D) that advances treatment innovation in the face of the growing global addiction crisis. Indivior has a long history of supporting the addiction treatment community and has been involved in manufacturing and supplying buprenorphine, a  $\mu$ -opioid receptor (MOR) partial agonist and  $\kappa$ -opioid receptor antagonist, for patients since 1996 as a treatment for OUD.

Indivior's focus on putting the patient first helps define the company's R&D mission: stabilizing drug delivery, decreasing dosing frequency, increasing treatment adherence and retention, decreasing diversion and misuse, improving management of overdose, and treating the comorbidities of addiction. Indivior's science is constantly expanding the mechanistic understanding of addiction to promote the development of novel approaches to treatment and new methodologies to support measurements of clinical response. To keep this promise, Indivior has recently invested in the construction of a state-of-the-art R&D Centre of Excellence in Hull, UK.

### Expanding access to opioid use disorder treatment

Indivior is developing BBP-6000, a new investigational buprenorphine sustained-release formulation that uses the ATRIGEL delivery system, which consists of a polymeric solution of a biodegradable poly-(DL-lactide-co-glycolide) co-polymer dissolved in *N*-methyl pyrrolidone (NMP), a water-miscible biocompatible solvent. After subcutaneous injection, NMP interacts with body fluids that replace the NMP as it diffuses out of the polymer matrix, triggering polymerization, which traps buprenorphine inside and forms an amorphous solid depot *in situ*. The depot releases buprenorphine over a one-month period by diffusion as the polymer biodegrades (Fig. 2).

BBP-6000 was designed to provide sustained plasma levels of buprenorphine that translate into high and sustained MOR occupancy in the brain over

a one-month period to suppress withdrawal symptoms and reduce the subjective and objective effects of opioid agonists.

RBP-6000 was granted Priority Review Designation and is currently under review by the US Food and Drug Administration. The results of Indivior's pivotal US phase 3 trial in subjects with moderate to severe OUD as part of a complete treatment plan that included counseling and psychosocial support showed that treatment with RBP-6000 significantly reduced illicit opioid use compared to placebo over a 6-month period. Treatment outcomes were consistent across other clinical endpoints, including control of craving and withdrawal symptoms. Furthermore, exposure-response analyses predicted correlation among buprenorphine plasma concentration, whole-brain MOR occupancy, abstinence, withdrawal, and opioid craving. The safety profile of RBP-6000 was consistent with the known profile of transmucosal buprenorphine, with the addition of injection-site reactions.

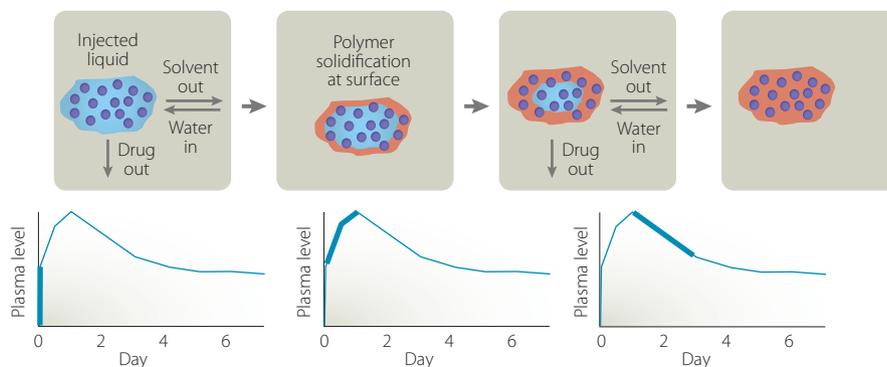
### Addressing the alcohol use disorder challenge

AUD is a chronic disease with a multifactorial etiology that is characterized by excessive drinking, alcohol craving, loss of control of alcohol intake, tolerance, and physical dependence, with a risk of potentially life-threatening alcohol withdrawal syndrome. According to the World Health Organization, the worldwide average level of alcohol consumption in 2016 was 6.4 L of pure alcohol per person aged 15 years or older<sup>2</sup>. This alcohol consumption resulted in about 3.3 million deaths, or 5.9% of all global deaths, and was responsible for 139 million DALYs, or 5.1% of the global burden of disease and injury<sup>2</sup>. These findings highlight the need for continued and increased efforts to reduce the harmful use of alcohol.

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Decades of research have focused on the way alcohol enhances inhibitory  $\gamma$ -aminobutyric acid (GABA)-mediated neurotransmission, including the characterization of drugs such as baclofen that target the GABA system<sup>3</sup>. True to its vision and mission, Indivior is developing arbaclofen placarbil, a novel transported prodrug of *R*-baclofen, the more active of the two baclofen enantiomers, that is designed to be well absorbed by the large intestine, thus allowing less frequent dosing and reduced fluctuations in the plasma. Results of an ongoing phase 1/2 clinical study of the bioavailability of arbaclofen placarbil will be available in early 2018.



**Figure 2: Indivior's RBP-6000 sustained-release formulation of buprenorphine.** RBP-6000 uses the ATRIGEL delivery system, a solution consisting of a biodegradable poly-(DL-lactide-co-glycolide) co-polymer dissolved in *N*-methyl pyrrolidone (NMP), a water-miscible biocompatible solvent. After subcutaneous injection, NMP interacts with body fluids that replace the NMP in the matrix, triggering polymerization. Buprenorphine trapped inside the polymer formed *in situ* is gradually released over a one-month period as the polymer biodegrades.

### Addressing drug use disorder psychiatric comorbidities

Epidemiological and clinical studies have shown that psychiatric disorders are highly comorbid with DUDs. For example, nearly half of patients diagnosed with schizophrenia, a chronic disorder characterized by a lifelong pattern of acute psychotic episodes superimposed on chronically poor psychosocial adjustment, have co-occurring DUDs<sup>4</sup>. Therefore, adherence to antipsychotic pharmacotherapy is a key aspect of treatment, and long-acting injectable antipsychotics may facilitate improvements in medication compliance, thereby reducing the risk of relapse and potentially facilitating the management of comorbid DUDs.

Indivior is developing a once-monthly sustained-release formulation of risperidone (RBP-7000) using the ATRIGEL delivery system for the long-term treatment of schizophrenia. The results of a pivotal phase 3 trial to assess the efficacy, safety and tolerability of RBP-7000 in subjects with acute schizophrenia showed clinically significant reductions in the symptoms of acute schizophrenia over an eight-week treatment period<sup>5</sup>.

### Expanding treatment opportunities on behalf of patients

Indivior continues the work of changing societal attitudes toward DUDs, revising their status from marginalized conditions to treatable diseases. Indivior contributes to widening access to quality treatments by educating health care professionals on treatment options and making sure patients know that treatment is available. The global challenge of DUDs also means that there are many more countries and addiction areas into which Indivior can expand to meet unmet patient needs.

Indivior invests in prospective health economics and outcomes research as part of clinical development plans to better understand patient outcomes beyond clinical efficacy and safety (e.g., improvement in health status and health-related quality of life, medication satisfaction, decreased health care resource utilization, improvement in employment status and health insurance, and decreases in comorbid drug use and psychiatric associations). Indivior is also focusing on new molecular targets with mechanisms of action involved in craving; these are likely to be useful across DUDs.

More collaborative research efforts will be required on the pharmacogenomics of DUDs, including learning how to characterize and quantify pharmacotherapy response (e.g., efficacy, nonadherence, treatment duration, concurrent medications use) and how to define patients' characteristics (e.g., differential diagnosis, illness course, comorbidities). Indivior believes that these concerted efforts may ultimately result in the reduction and cessation of drug use by the patient, thereby preventing future harms associated with the abuse of drugs and improving the quality of life and well-being of patients with DUDs.

"The inherent complexity and multi-dimensional nature of DUDs require a deep understanding of their neurobiological underpinnings," said Heidebreder. "Equally important are partnerships and collaborations that allow us to understand patients' unmet needs and accelerate the development of new medications. Indivior's mission is to facilitate these coordinated efforts to offer innovative solutions and ultimately prevent and treat DUDs and their comorbidities. Patients are waiting."

1. United Nations Office on Drugs and Crime. *World Drug Report 2017: Executive Summary* (United Nations, 2017).
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