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MUNDIPHARMA RESEARCH
International Research & Development

Mundipharma: pioneering innovations in pain management

The Mundipharma international network: thinking differently about pain

Pain, both acute and chronic, can be a debilitating disorder and is a recognized global health-care problem[1]. More than half of people who experience trauma or undergo surgery subsequently have severe to intolerable acute pain, which can lead to numerous adverse physiological consequences[1]. Moreover, approximately 1 in 5 adults have chronic pain, with many of these people experiencing severe pain[1,2]. Pain impairs patients' everyday activities and social functions; severe neuropathic pain is particularly associated with poor health-related quality of life[2]. Pain also places considerable burden on health services and the economy[2]. Unfortunately, many patients do not have access to appropriate care. In a Europe-wide survey of patients with chronic pain, 40% said that their pain was inadequately managed and about 30% said that they were not receiving any treatment for their pain[3]. Furthermore, the aetiology of some disorders associated with pain, such as fibromyalgia syndrome, is poorly understood, making it difficult to find effective treatments[4]. In response to these and other challenges, Mundipharma is thinking differently about pain by recognizing opportunities to help patients whose pain is poorly managed, and pioneering research where there are unmet needs. Our goal is to provide treatments that will re-address the pain–life balance — shifting people's experiences away from pain and back towards the enjoyment of life.

Mundipharma, and its global network of independent associated companies, was founded by physicians in 1952. The Mundipharma network has a strong background in pain management and has pioneered the introduction of innovative treatments for pain, including drugs with abuse-deterrent properties and novel drug formulations. As shown in Figure 1, the Mundipharma network is active in more than 50 countries around the world. This network has helped to deliver a number of innovative pain treatments to the clinic, developed both internally and through global strategic alliances. Mundipharma's dedicated research and development organization, based in Europe (Cambridge, UK, and Limburg, Germany), works on behalf of the network and in collaboration with other companies to bring new treatments to patients. It carries out early- and late-stage pre-commercial development, including preclinical research, clinical development, drug safety and regulatory affairs.

Mundipharma's heritage in pain stretches over five decades. It developed the world's first prolonged-release morphine sulphate tablet, which was introduced into clinical practice in 1980. This innovation helped to shape the modern-day management of cancer pain, with prolonged-release morphine sulphate becoming a step III treatment option in the World Health Organization's (WHO) pain relief ladder for cancer care in 1986[5,6]. Since then, Mundipharma has continued to strive to support new standards in pain management, bringing a range of innovative treatments to the clinic that include prolonged-release oxycodone for patients with severe pain, the first 7-day analgesic patch (containing buprenorphine) and the first opioid agonist/antagonist combination tablet (prolonged-release oxycodone/naloxone).

Mundipharma's comprehensive portfolio of pain treatments now includes more than 15 different products comprising immediate- and controlled-release tablets and various other formulations (for example, capsules, injections and patches) that have been designed to meet different patients' needs (Figure 2). Our expertise in the management of pain, as well as a growing pipeline of first-in-class compounds — including a selective sigma-1 antagonist for neuropathic pain and a co-crystal of tramadol and celecoxib for acute pain — highlight Mundipharma's continuing commitment to the advancement of pain treatment. We are also aware that pain management is not just about 'the pill'. Indeed, increasing understanding of how pain impacts the lives of patients is crucial to solving the problem of pain. Through collaborations with health-care professionals, non-governmental organizations and patients, Mundipharma has helped to develop tools such as websites to support and foster education in pain management, raise public awareness of pain management and provide patient support.

Re-addressing the pain–life balance

Prolonged-release oxycodone/naloxone and the 7-day buprenorphine patch are innovative opioid preparations that illustrate

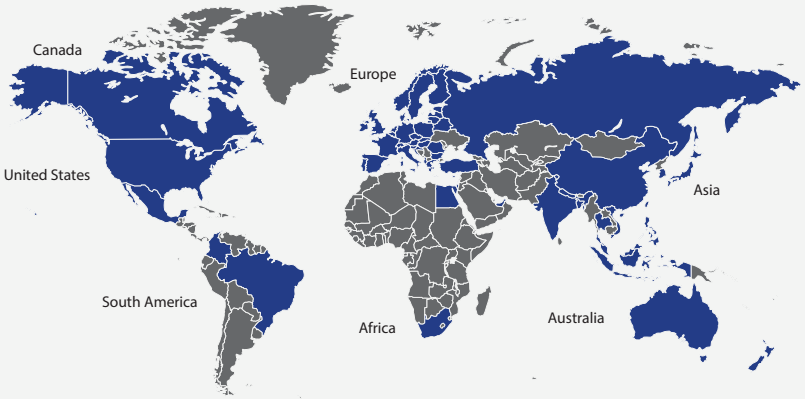

Figure 1 | The Mundipharma network. More than 50 independent associated companies make up Mundipharma's international network.

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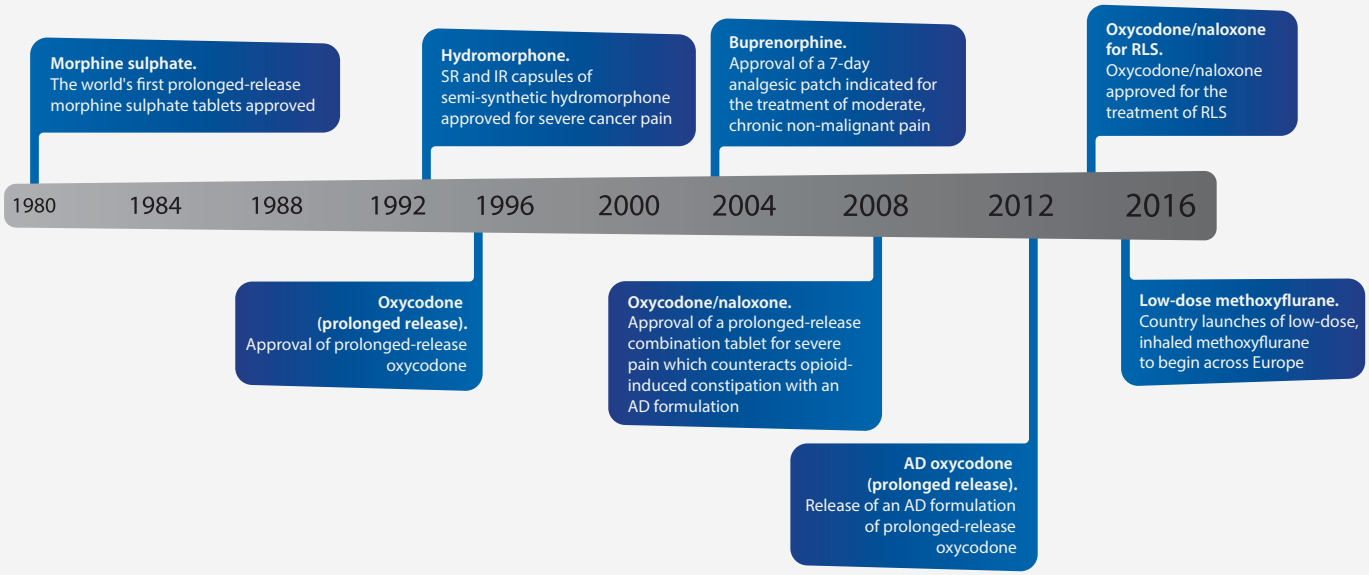

Figure 2 | Mundipharma's timeline. Pain and associated innovations that have been developed, or co-developed, by the Mundipharma network of independent associated companies. AD, abuse deterrent; IR, immediate-release; RLS, restless legs syndrome; SR, slow-release.

Mundipharma's approach to re-addressing the pain–life balance. The transdermal patch was developed to provide patients with continuous delivery of buprenorphine and a consistent plasma drug concentration for seven days with one application[7].

Prolonged-release oxycodone/naloxone was developed to address a key limitation of opioid agonists; namely, their association with a high incidence of opioid-induced constipation and related health problems, which can impact quality of life and lead to dose reductions or treatment cessation, thereby limiting pain management[8]. The combination of a strong opioid agonist (oxycodone) with the opioid antagonist naloxone, in an oral prolonged-release tablet, provides analgesia while simultaneously reducing the risk of opioid-induced constipation[9]. The naloxone component is also expected to provide abuse-deterrent properties.

Overall, more than 30 phase I to III clinical studies have been conducted with prolonged-release oxycodone/naloxone. As part of Mundipharma's endeavours to provide pain solutions for populations for which pain is not well managed, Mundipharma led the first randomized, double-blind, controlled trial specifically designed to investigate the treatment of pain in Parkinson's disease[10]. This has prompted studies that investigate whether pain treatments might have a role in indications other than pain, particularly in neurological disorders. A pivotal phase III trial revealed that prolonged-release oxycodone/naloxone can bring symptomatic relief to patients with severe restless legs syndrome (RLS) that was inadequately controlled by previous treatments; it subsequently became the first opioid to be granted a licence in Europe for the treatment of RLS[11,12]. Preliminary data, which provide mechanistic support for the treatment of RLS with opioids, are now being explored by Mundipharma in collaboration with the University of Florida.

Through further collaborations with leading academic institutions, Mundipharma is striving to increase understanding of the role of opioids in pain management and to identify further opportunities to impact the pain–life balance. A study with Barts Health NHS Trust in London is using gene expression profiling to investigate the effect of different opioid preparations on immunomarkers. Moreover, Mundipharma is supporting a team at the Rambam Health Care Campus, Israel Institute of Technology that is investigating psychophysical as well as genetic and neuroimaging biomarkers for opioid-induced hyperalgesia in patients with chronic neuropathic pain. The study aims to provide a way to identify patients who might be at risk of poor outcomes with opioid therapy. Mundipharma, alongside researchers at the Division of Neurological Pain Research and Therapy at the University Medical Centre Schleswig-Holstein, Kiel, is also developing an easy-to-use, bedside quantitative sensory testing battery to enable patient stratification by somatosensory phenotyping in neuropathic pain trials.

Paving the way for patient access

By thinking differently about pain — and because of our global network and partnerships with other companies and stakeholders — Mundipharma is able to build on its research and bring novel treatments to patients who need them the most. This is illustrated by the alliance between Mundipharma and Medical Developments International. This alliance will introduce low-dose methoxyflurane to Europe; this treatment is self-administered through an inhaler and has been used clinically in Australia. It is now licensed in several European countries, including France and Belgium, for the emergency relief of moderate to severe pain associated with trauma[13]. Mundipharma are preparing to explore further indications for inhaled methoxyflurane; phase III trials for procedural pain and for paediatric use are planned.

Mundipharma understands that patients can only benefit from medicines that they can access. We recognize the constraints of governmental budgets and speak to payers, regulators and clinicians in the early stages of product development to understand what they want in order to deliver treatments that will not only be approved, but also be welcomed by the market. Cost-effective solutions are likely to arise as a result of developing innovative therapies to tackle the pain–life balance and overcome the shortcomings of earlier treatments. Indeed, Mundipharma supports studies to assess cost-effectiveness, and our treatments have shown potential economic benefits[14–17]. Only by working together with other companies and stakeholders — sharing ideas and challenging each other — can we make the most of our pain assets.

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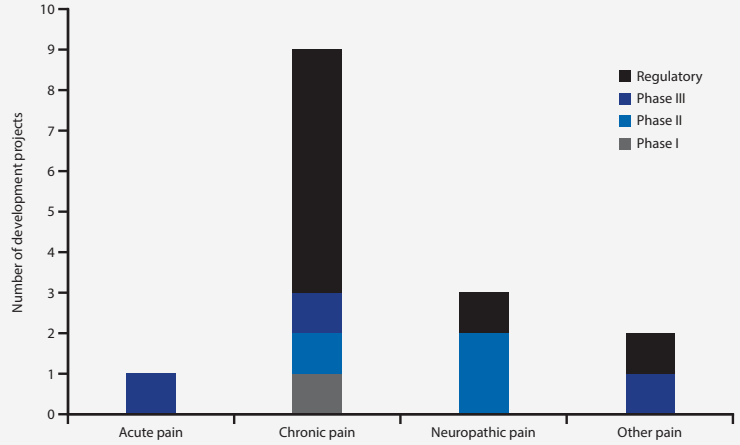

Figure 3 | Mundipharma's pipeline. An overview of the current projects of the Mundipharma network of independent associated companies.

Looking to the future

Mundipharma is open to research enquiries and is actively exploring opportunities to translate promising early-stage developments into innovative clinical pain therapies. In 2014, Mundipharma began a global, multi-programme discovery and development collaboration with ESTEVE to bring to market important next-generation products for the management of pain. This collaboration leverages each company's individual strengths — it combines Mundipharma's expertise in the development and commercialization of novel pain treatments with ESTEVE's extensive pain-focused drug discovery and research capabilities. The assets covered by the collaboration include E-52862/MR309 and Co-Crystal of Tramadol-Celecoxib (CTC; CTC is being developed by ESTEVE and Mundipharma as E-58425/MR308). E-52862/MR309 is a first-in-class selective sigma-1 antagonist that represents a novel approach and a new mechanism of action for treating pain. It is in phase II clinical trials for neuropathic pain and has the potential to tackle the lack of efficacy and tolerability that some patients experience with current neuropathic pain treatments. The unique mechanism of action also supports the potential combination with other analgesic compounds to enhance pain control. CTC is a first-in-class active pharmaceutical ingredient (API)-API co-crystal formed by tramadol (a μ-opioid agonist and inhibitor of serotonin and noradrenaline reuptake) and celecoxib (an inhibitor of cyclooxygenase-2) and is being developed as a treatment for moderate-to-severe acute pain. Co-crystallization of tramadol and celecoxib in CTC changes the physicochemical and pharmacokinetic properties of the constituent APIs[18]. Results from phase I/II studies suggest that the unique structure of CTC may lead to improved pharmacokinetic profiles for each component and could provide a new treatment option for acute pain[18]. The collaboration between Mundipharma and ESTEVE will see CTC progress into international phase III trials. Additional early-stage collaborations are in progress to identify further novel targets in pain that could pave the way for new treatments. These partnerships expand Mundipharma's pain expertise beyond opioids to treatments for neuropathic, acute and moderate pain, as well as for chronic pain (Figure 3).

Mundipharma has a proven track record of bringing pain innovations to those who need them most, successfully launching several pain products over recent decades. By using our expert knowledge and experience of pain, Mundipharma intends to build on this background as part of an ongoing commitment to the field. We will achieve this by investigating novel treatments and improving existing treatments, with a focus on neuropathic pain as well as other areas for which there is an unmet medical need. By developing these treatments through alliances with research organizations, health-care professionals and patients, we hope to continue to improve and expand pain treatment options throughout the world.

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