# NEW DATA HIGHLIGHT POTENTIAL ADVANTAGES OF CTC (CO-CRYSTAL* OF TRAMADOL-CELECOXIB) OVER TRAMADOL ALONE

- New data, presented for the first time at the 16th World Congress on Pain, demonstrate the clinical potential of a new analgesic recently added to the Mundipharma pain pipeline
- Co-Crystal of Tramadol and Celecoxib (CTC), specifically designed by merging two well-established analgesics into a new co-crystal structure, was shown in a phase II clinical study to achieve effective pain relief at lower doses compared to tramadol alone, and with an improvement in overall tolerability[1]
- Pre-clinical and PK studies have shown that co-crystallising tramadol and celecoxib into CTC optimises the physicochemical properties of the components to demonstrate synergy and enhanced PK profiles respectively[2,3,4]
- Despite advances in pain research over many decades, there is still an urgent need to develop new analgesics that are both effective and well tolerated

**Cambridge, UK, 29 September 2016** – New data presented for the first time at the 16th World Congress on Pain in Yokohama, Japan, have demonstrated potential advantages of the first in class analgesic co-crystal in acute pain over tramadol alone. Results from a Phase II study have shown that CTC (Co-Crystal of Tramadol-Celecoxib) 100 mg, 150 mg and 200 mg† (which contain tramadol 44 mg, 66 mg and 88 mg, respectively) provided superior pain relief to tramadol (100 mg) in patients with moderate to severe pain after tooth extraction. Dose dependent pain relief with CTC was found to be associated with similar (CTC 200 mg), or better (CTC 50 mg, 100 mg and 150 mg) tolerability than tramadol 100 mg alone.[1]

These clinical benefits can be explained from the results of:

- Dissolution studies which have demonstrated a changed, potentially clinically beneficial release profile of celecoxib (by increasing its solubility) and tramadol (by lowering its peak concentration), with anticipated translation into optimised pharmacokinetics[5]
- A pre-clinical study in rats, which showed that $ctc_{susp}$ (Co-Crystal of Tramadol-Celecoxib in a molecular ratio of 1:1 in suspension) provided synergy in a postoperative pain model without enhancing adverse effects[2]

* co-crystals are crystalline solids of two or more molecular compounds in a stoichiometric ratio, which are neither solvates nor simple salts; if at least one of its molecular components is an active pharmaceutical ingredient (API) then it is recognised as a pharmaceutical co-crystal

† CTC 100 mg is equivalent to 44 mg tramadol + 56 mg celecoxib; CTC 150 mg is equivalent to 66 mg tramadol + 84 mg celecoxib; CTC 200 mg is equivalent to 88 mg tramadol + 112 mg celecoxib

- Pharmacokinetic (PK) studies, which showed that co-crystallising tramadol and celecoxib into CTC led to a changed, potentially clinically beneficial PK profile for each active pharmaceutical ingredient (API) (tramadol and celecoxib) compared with commercially available tramadol and celecoxib given as an open combination.[3] Administration of CTC was associated with a reduced tramadol peak plasma concentration, and a shorter time to reaching maximum peak plasma concentration of celecoxib[4]

Together the available study data suggest that CTC may provide effective analgesia at lower doses of each component, with a potential for an improvement in tolerability, and earlier onset of pain relief compared to tramadol alone.[3,4]

CTC is a first in class analgesic co-crystal with a molecular ratio of 1:1 of tramadol hydrochloride and celecoxib. CTC has been developed to capitalise on the complementary mechanisms of action of the well-known analgesics tramadol and celecoxib. Co-crystallising both constituents into CTC optimises their pharmacokinetic characteristics compared with currently marketed tramadol, celecoxib, or their concomitant administration in open combination.

“We are very excited by the results of these CTC studies,” said Mundipharma International Head of Medical Affairs for Pain, Dr Harry Smith. “By optimising the pharmacokinetic characteristics of tramadol and celecoxib in CTC, we have been able to demonstrate that CTC achieves effective analgesia at lower doses compared to tramadol, and with an improvement in overall tolerability,” Dr Smith explained.

Acute pain benefits from a multimodal approach for effective pain treatment.[6] CTC represents a rational approach of combining well-established and efficacious analgesics, which act through complementary anti-nociceptive and anti-inflammatory pathways.

Intense acute pain afflicts millions of patients each year.[6] Despite many advances in pain research over the last few decades, inadequate control of acute pain, for example in trauma patients and following surgery, is still a common problem.[6,7,8,9]

Poor management of acute pain prevents patients from leading a normal life, and results in repeat visits to the emergency department or family doctor.[6,10] Poor pain management puts patients at risk of many different complications, creates needless suffering, and also significantly increases costs of care.[7] There is good evidence to show that poorly managed acute pain can evolve into chronic disabling pain. For up to 20% of patients, poor management of acute post-operative pain could lead to severe chronic pain.[7]

Although opioids are the preferred treatment for most moderate to severe acute pain, their side effects can impede their use, and thus, their clinical effectiveness. Opioids in therapeutic doses

may cause sedation, dizziness, nausea, vomiting, constipation, tolerance, and respiratory depression.[11]

CTC has been specifically designed by merging two well-established analgesics into a new co-crystal structure with an optimised pharmacokinetic profile, thereby achieving effective pain relief at lower doses compared to tramadol alone, and with an improvement in tolerability.

"Mundipharma is committed to developing new treatments to help patients better manage their pain, which remains an area of continuing unmet need," said Dr Smith. CTC is already proving to be an important asset in the Mundipharma pain pipeline, with Phase III trials now underway," Dr Smith concluded.

**-Ends-**

**Notes to editors:**

***About CTC***

CTC is in development for use in patients with moderate to severe acute pain. CTC is part of a global‡ discovery and development collaboration between Mundipharma and its independent associated companies with Laboratorios del Dr. Esteve, S.A.U. (ESTEVE). The collaboration is designed to bring to market next generation pain products, which will reduce the severe negative impact pain currently has on both patients and health systems.

***About Mundipharma***

Mundipharma and its network of independent associated companies are privately owned companies and joint ventures covering the world's pharmaceutical markets. These companies are committed to bringing to patients the benefits of significant new treatment options in the core therapy areas of pain, respiratory, addiction, oncology and inflammatory conditions. Through innovation, design and acquisition, Mundipharma delivers important treatments to meet the most pressing needs of patients, healthcare professionals and health systems worldwide. For further information, please visit: www.mundipharma.com

***About ESTEVE***

ESTEVE is a leading pharmaceutical chemical group based in Barcelona, Spain. Since it was founded in 1929, ESTEVE has been firmly committed to excellence in healthcare, dedicating efforts to innovative R&D of new medicines for unmet medical needs and focusing on high science and evidence-based research. ESTEVE has a strong partnership approach to drug discovery, development and commercialisation. The company works both independently and in collaboration to bring new, differentiated best-in-class treatments to patients who need them. The company currently employs 2,300 professionals and has subsidiaries and production facilities in several European countries, USA, China and Mexico. More about ESTEVE at www.esteve.com and www.esteve.com/research-development

‡ Excluding the US

**For further information, please contact:**

Carolin Prasmo
carolin.prasmo@auroracomms.com
T: +44 20 7148 3628

Rachel Terry
rachel.terry@auroracomms.com
T: +44 20 7148 4186

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