A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of the Extended-Release Tramadol Hydrochloride/Acetaminophen Fixed-Dose Combination Tablet for the Treatment of Chronic Low Back Pain

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ABSTRACT

Background: Chronic low back pain is a common condition that is often difficult to treat. The combination of tramadol hydrochloride and acetaminophen in an extended-release formulation has been shown to provide rapid and long-lasting analgesic effects resulting from the synergistic activity of these 2 active ingredients.

Objective: The goal of this study was to evaluate the efficacy and safety of extended-release tramadol hydrochloride 75-mg/acetaminophen 650-mg fixed-dose combination tablets (TA-ER) for the treatment of chronic low back pain.

Methods: This Phase III, double-blind, placebo-controlled, parallel-group study enrolled 245 patients with moderate to severe ($\geq$4 cm on a 10-cm visual analog scale) chronic ($\geq$3 months') low back pain insufficiently controlled by previous NSAIDs or cyclooxygenase-2–selective inhibitors and randomly assigned them to receive 4 weeks of either TA-ER or placebo. The primary efficacy end point was the percentage of patients with a pain intensity change rate $\geq$30% from baseline to final evaluation. Secondary end points included quality of life (Korean Short Form–36), functionality (Korean Oswestry Disability Index), and adverse events.

Results: The percentage of patients with a pain intensity change rate $\geq$30% was significantly higher ($P < 0.05$) in the TA-ER group than in the placebo group for both the full analysis set and the per-protocol population. Pain relief success rate from baseline was significantly higher with TA-ER versus placebo at days 8 and 15 but not at the final visit. Patients in the TA-ER group had significant improvements versus placebo in role–physical, general health, and reported health transition domains of the Korean Short Form–36 and significantly higher functional improvements in the personal care section of the Korean Oswestry Disability Index. Patient assessment of overall pain control as "very good" was also significantly higher with TA-ER than with placebo. Adverse events were reported more frequently with TA-ER than with placebo; the most common adverse events reported were nausea, dizziness, constipation, and vomiting.

Conclusions: TA-ER was significantly more effective than placebo in providing pain relief, functional improvements, and improved quality of life. It exhibited a predictable safety profile in patients with chronic low back pain. ClinicalTrials.gov identifier: NCT01112267. (*Clin Ther*. 2013;35:1830–1840)

Key words: adverse event, chronic low back pain, extended-release tramadol HCl/acetaminophen fixed-dose combination, functional improvement, pain relief.

INTRODUCTION

Low back pain is a common condition, with a lifetime risk exceeding 70% in industrialized countries,[1–4] and it represents a leading cause of disability and days

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missed from work.[5] Although peripherally acting NSAIDs have demonstrated efficacy for short-term relief of acute low back pain, their efficacy against chronic low back pain is unclear.[6,7] In contrast, centrally acting antidepressants (eg, duloxetine) and other drugs (eg, tramadol) have shown efficacy in patients with chronic back pain.[8–13] Tramadol is a centrally acting analgesic with a dual mechanism of action: inhibition of serotonin and noradrenaline reuptake, and nonselective activation of μ-opioid receptors via the active metabolite *O*-desmethyltramadol (M1).[14] Acetaminophen has been used as a first-line treatment choice for chronic pain because it has analgesic and antipyretic properties, provides good safety and tolerability, and rarely generates hepatotoxicity at therapeutic doses; however, its misuse is associated with liver damage.[15–17] Although acetaminophen has an unclear mechanism of action and site of pain action, the drug may modulate or inhibit a pain mediator in the peripheral sites of injuries,[18] and its analgesic effects mainly occur in the spinal or supra-spinal levels of the central nervous system.[19] A rational strategy in the pharmacologic treatment of chronic low back pain is to combine agents with proven efficacy that would exhibit multiple analgesic mechanisms of action.

Tramadol hydrochloride (HCl)/acetaminophen tablets* (37.5 mg/325 mg) offer a more rapid onset of analgesia than with tramadol alone because of the action of acetaminophen,[20] and reports indicate that the combined use of tramadol and acetaminophen demonstrate a synergistic effect in animal models.[21] Given their effective pain relief and good tolerability, immediate-release tramadol/acetaminophen tablets are often used for the treatment of chronic low back pain.[19,22–24] However, analgesic effects last ~6 hours, and patients are likely to develop low treatment compliance because they may find it inconvenient to take the tablets ~4 times a day to maintain a certain concentration level within the body. In particular, patients can experience end-of-dosing pain when the concentration in the blood falls below therapeutic levels. Accordingly, it was necessary to develop an extended-release formulation with similar pain relief effects but with sustained analgesic activity over a longer period of time.

*Trademark: Ultracet® (Janssen-Ortho, LLC, Gurabo, Puerto Rico).

Extended-release tramadol HCl 75-mg/acetaminophen 650-mg fixed-combination tablets† (TA-ER) were developed to meet this clinical need and are currently being investigated as a pain reliever, generating fast-acting and continuous analgesic effects for up to 12 hours because of the synergistic effect of the 2 active ingredients.[25] The purpose of the present multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase III clinical trial was to evaluate the efficacy and safety of TA-ER for the treatment of moderate to severe chronic low back pain insufficiently controlled by previous NSAIDs or cyclooxygenase-2 (COX-2)–selective inhibitors.

PATIENTS AND METHODS

Eligible patients were between 25 and 75 years of age, able to walk, had moderate to severe chronic low back pain (average pain intensity ≥4.0 cm on a 10-cm visual analog scale [VAS], where 0 cm = no pain to 10 cm = worst pain imaginable) despite the use of NSAIDs or COX-2–selective inhibitors, and had pain severe enough to require continual use of analgesics for at least 3 months before screening. Patients were required to have taken a stable dose of NSAIDs or COX-2–selective inhibitors from 7 days before study drug administration (screening period) and to maintain that same dose during the study period. Exclusion criteria included failure or discontinuation of tramadol or tramadol/acetaminophen treatment in the past due to an adverse event; or the ingestion of tramadol, tramadol/acetaminophen, or opioid analgesics within 30 days of study drug administration, acetaminophen within 7 days of study drug administration, or antidepressants, anticonvulsants, or cyclobenzaprine (for pain relief) within 3 weeks of study drug administration. Patients were also excluded if they had a tumor or infection on the meninges or spinal cord; had more severe pain in an area other than the low back; had a neurologic deficit on the legs due to a spine lesion; suffered from pain due to fibromyalgia, complex regional pain syndrome, acute spinal cord compression, cauda equina syndrome, proximal diabetic neuropathy, infection, or a tumor; underwent back surgery within the past 3 months; or received a steroid injection within 4 weeks of screening.

†Extended-release tramadol hydrochloride 75-mg/acetaminophen 650-mg fixed-combination tablets (Janssen Korea, Ltd, Yongsan-Gu Seoul, Korea).