Long-Term Safety and Efficacy of Tapentadol Extended Release Following up to 2 Years of Treatment in Patients With Moderate to Severe, Chronic Pain: Results of an Open-Label Extension Trial

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ABSTRACT

Purpose: Tapentadol extended release (ER) has demonstrated efficacy and safety for the management of moderate to severe, chronic pain in adults. This study evaluated the long-term safety and tolerability of tapentadol ER in patients with chronic osteoarthritis or low back pain.

Methods: Patients were enrolled in this 1-year, open-label extension study after completing one of two 15-week, placebo-controlled studies of tapentadol ER and oxycodone controlled release (CR) for osteoarthritis knee pain (NCT00421928) or low back pain (NCT00449176), a 7-week crossover study between tapentadol immediate release and tapentadol ER for low back pain (NCT00594516), or a 1-year safety study of tapentadol ER and oxycodone CR for osteoarthritis or low back pain (NCT00361504). After titrating the drug to an optimal dose, patients received tapentadol ER (100–250 mg BID) for up to 1 year (after finishing treatment in the preceding studies); patients who were previously treated with tapentadol ER in the 1-year safety study received tapentadol ER continuously for up to 2 years in total.

Findings: Of the 1,154 patients in the safety population, 82.7% were aged >65 years and 57.9% were female; 50.1% had mild baseline pain intensity. Mean (SD) pain intensity scores (11-point numerical rating scale) were 3.9 (2.38) at baseline (end of preceding study) and 3.7 (2.42) at end point, indicating that pain relief was maintained during the extension study. Improvements in measures of quality of life (eg, EuroQol-5 Dimension and the 36-item Short Form Health Survey [SF-36]) health status questionnaires) achieved during the preceding studies were maintained during the open-label extension study. Tapentadol ER was associated with a safety and tolerability profile comparable to that observed in the preceding studies. The most common treatment-emergent adverse events (incidence ≥10%; n = 1154) were headache (13.1%), nausea (11.8%), and constipation (11.1%). Similar efficacy and tolerability results were shown for patients who received up to 2 years of tapentadol ER treatment.

Implications: Pain relief and improvements in quality of life achieved during the preceding studies were maintained throughout this extension study, during which tapentadol ER was well tolerated for the long-term treatment of chronic osteoarthritis or low back pain over up to 2 years of treatment. (ClinicalTrials.gov identifier: NCT00487435.) (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮) © 2015 Published by Elsevier HS Journals, Inc.

Key words: chronic pain, extension study, low back pain, osteoarthritis pain, tapentadol ER.

INTRODUCTION

Opioid analgesics have demonstrated efficacy for the management of moderate to severe, chronic osteoarthritis

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pain,[1–3] as well as low back pain,[1,4,5] and are recommended for the management of chronic pain in patients who have failed to respond to other analgesics.[3,6,7] However, strong evidence regarding the efficacy of opioid analgesics for the long-term management of chronic nonmalignant pain is scarce.[4,8,9] Long-term pain management with opioids can be limited by the occurrence of adverse effects, such as nausea, vomiting, and constipation.[10] These adverse effects may lead patients to stop taking their opioid analgesics,[11] resulting in a disruption of pain relief. Physicians may also be hesitant to prescribe opioids for the management of chronic pain because of the risk of tolerance development and dependence and the risk of adverse effects associated with long-term opioid therapy.[12]

Tapentadol is a centrally acting analgesic that has μ-opioid receptor agonist and norepinephrine reuptake inhibitor activities, both of which contribute to its analgesic efficacy.[13–15] Phase III studies have shown the efficacy and safety of tapentadol extended release (ER; 100-250 mg BID) for the management of moderate to severe, chronic pain.[16–25] Tapentadol ER has been evaluated in patients with chronic osteoarthritis pain,[16–18,24] low back pain,[17–19,24] neuropathic pain associated with diabetic peripheral neuropathy,[20,25] and tumor-related pain.[21–23]

The objective of the present 1-year, Phase III, open-label extension study was to characterize the long-term safety and tolerability profile of tapentadol ER (100–250 mg BID) in patients with moderate to severe, chronic osteoarthritis hip or knee pain or low back pain. The study also evaluated withdrawal symptoms after discontinuation of tapentadol ER and the effects of tapentadol ER treatment on pain intensity, health status measures, and sleep quality and duration.

PATIENTS AND METHODS

The protocol and amendments of this study were reviewed by independent ethics committees and institutional review boards. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients signed an informed consent document to confirm that they understood the study purpose and procedures and were willing to take part in the study.

Patients

This 1-year, open-label extension study (NCT00487435) included patients who had completed 1 of the 4 following studies: a 15-week, randomized, double-blind, placebo-controlled, Phase III study that evaluated the efficacy of tapentadol ER and oxycodone controlled release (CR) for moderate to severe, chronic osteoarthritis knee pain (NCT00421928)[16]; a 15-week, randomized, double-blind, placebo-controlled, Phase III study that evaluated the efficacy of tapentadol ER and oxycodone CR for moderate to severe, chronic low back pain (NCT00449176)[19]; a 7-week, randomized, double-blind, Phase IIIb, crossover study that evaluated dose conversion between tapentadol immediate release and tapentadol ER for patients with moderate to severe, chronic low back pain (NCT00594516)[26]; or a 1-year, randomized, open-label, Phase III study that evaluated the long-term safety of tapentadol ER and oxycodone CR for moderate to severe, chronic osteoarthritis hip or knee pain or low back pain (NCT00361504).[18] Details of the methods and results of these studies have been published previously.[16,18,19,26] Patients were willing to take tapentadol ER and rescue medication (acetaminophen) for the duration of the extension study. Patients who were expected to require major surgery during the study and patients who had a clinically significant disease or a condition in addition to osteoarthritis or low back pain that could affect efficacy or safety assessments were excluded from the study.

Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors were permitted if prescribed for a reason other than pain (ie, depression) at a controlled, stable dose for at least 30 days before screening for the extension study. Benzodiazepines, mood stabilizers (used as minor tranquilizers or hypnotics), anti-Parkinsonian drugs, and anticonvulsants were permitted for patients who were on a controlled, stable dose for at least 30 days before screening. Transcutaneous electrical nerve stimulation, acupuncture, and other similar interventional adjunctive therapies were permitted during the study for patients who had been on regular therapy for at least 14 days. Acetylsalicylic acid ($\leq$325 mg/d orally) was allowed for cardiac prophylaxis. The occasional, limited use of NSAIDs for reasons other than chronic pain (eg, toothache, headache, fever) was allowed; patients were required to discuss any NSAID use with the investigator. All other analgesics except for tapentadol ER and specified doses of acetaminophen (see "Study Design") were prohibited during the study. Neuroleptics and monoamine oxidase inhibitors were prohibited within 14 days of screening and throughout the study; systemic corticosteroids were also prohibited throughout the study.

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