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## Drug Monograph

**Generic Name:** tapentadol extended-release

**Trade Name:** Nucynta ER<sup>®</sup>

**Dosage Form:** Extended-release tablets

**National Drug Codes (NDC#):** 50 mg 50458-860-01, 50458-860-02; 100 mg 50458-861-01, 50458-861-02; 150 mg 50458-862-01, 50458-862-02; 200 mg 50458-863-01, 50458-863-02; 250 mg 50458-864-01, 50458-864-02

**Manufacturer:** Depomed, Inc.

**ADF Product Classification:** Not Applicable

### Executive Summary

Nucynta ER<sup>®</sup> (tapentadol extended-release) is an extended-release (ER) formulation of tapentadol that is approved by the Food and Drug Administration (FDA) to treat pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Nucynta ER<sup>®</sup> (tapentadol extended-release) is also FDA-approved to treat neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.<sup>1,2</sup> Recommended initial dosing for Nucynta ER<sup>®</sup> (tapentadol extended-release) as the first opioid analgesic is 50 mg every 12 hours. The manufacturer does not provide specific conversion factors or initial dosing for patients converting to Nucynta ER<sup>®</sup> (tapentadol extended-release) from other opioids.<sup>1</sup> Nucynta ER<sup>®</sup> (tapentadol extended-release) contains tapentadol which is a  $\mu$  opioid receptor agonist and norepinephrine reuptake inhibitor. Both properties are thought to contribute to the analgesic effects of tapentadol.<sup>1-4</sup> Nucynta ER<sup>®</sup> (tapentadol extended-release) is being evaluated by the Drug Formulary Commission to determine if properties of the drug and formulation merit inclusion on the Massachusetts formulary of therapeutically equivalent substitutions, as outlined in Chapter 258 of the Acts of 2014.

The efficacy and safety of Nucynta ER<sup>®</sup> (tapentadol extended-release) was established in two phase III clinical trials in chronic low back pain (LBP) and osteoarthritis (OA) of the knee.<sup>5,6</sup> For DPN, the safety and efficacy of Nucynta ER<sup>®</sup> (tapentadol extended-release) was established in two phase III clinical trials.<sup>7,8</sup> The long-term tolerability and safety of Nucynta ER<sup>®</sup> (tapentadol extended-release) was established in two extension studies of one year in length, the second of which was an extension study in patients that had already been treated for up to one year with Nucynta ER<sup>®</sup> (tapentadol extended-release).<sup>9,10</sup> Nucynta ER<sup>®</sup> (tapentadol extended-release) has also been evaluated in patients with chronic cancer-related pain (CCP), and was found to be a relatively safe and effective treatment option in CCP.<sup>11,12</sup>

Nucynta ER<sup>®</sup> (tapentadol extended-release) is not approved as an abuse-deterrent formulation (ADF); however, *in vitro* laboratory manipulation and extraction studies and clinical abuse potential studies have been performed.<sup>13,14</sup> Attempts to crush or break the Nucynta ER<sup>®</sup> (tapentadol extended-release) tablet resulted in minimal deformation with every method used, with the exception of using a hammer in the laboratory manipulation study. Hammering Nucynta ER<sup>®</sup> (tapentadol extended-release) tablets resulted in flattening of tablets, but no pulverization. Flattened Nucynta ER<sup>®</sup> (tapentadol extended-release) tablets were susceptible to release of over 50% of drug upon dissolution with vigorous shaking over an extended period of time. In addition, flattened tablets had a faster release profile compared to intact tablets with 30% of drug released after 30 minutes; however, *in vivo* data such as time to peak serum concentration ( $T_{max}$ ) for the flattened tablets is unavailable due to the nature of the study.<sup>13</sup> Clinical abuse potential studies revealed that recreational opioid users generally had more difficulty altering the Nucynta ER<sup>®</sup> (tapentadol extended-release) dosage form than a non-ADF oxycodone ER tablet, and the subjects were more willing to abuse the powder made from tampering with the non-ADF oxycodone ER tablet.<sup>4</sup>

Postmarketing survey data indicates there is a relatively low level of abuse of tapentadol immediate-release; however, it is not clear if this is a function of availability or the medication itself. There is currently a lack of published postmarketing data related to the abuse of Nucynta ER<sup>®</sup> (tapentadol extended-release).<sup>2</sup> One postmarketing survey study indicated that Nucynta ER<sup>®</sup> (tapentadol extended-release) abuse was reported significantly less frequently than all other long-acting comparators with the exception of hydromorphone ER; however, the survey was conducted from January 2011 to September 2012, and Nucynta ER<sup>®</sup> (tapentadol extended-release) was not approved in the United States until August 2011.<sup>15</sup>

Potential strengths of Nucynta ER<sup>®</sup> (tapentadol extended-release) include the novel mechanism of action and a potentially favorable adverse effect profile relative to the opioid class. Potential weaknesses of Nucynta ER<sup>®</sup> (tapentadol extended-release) include cost, potential for drug-drug interactions with antidepressants and inability to exceed 500 mg per day, which may not provide adequate analgesia for patients that require high doses of opioids for conditions such as cancer-related pain. Similar to all other long-acting opioids, Nucynta ER<sup>®</sup> (tapentadol extended-release) is subject to requirements of the shared system Extended-Release and Long-Acting (ER/LA) Risk Evaluation and Mitigation Strategies (REMS) program.<sup>16</sup>

**Reference Data**

Nucynta ER<sup>®</sup> (tapentadol extended-release) is a long-acting formulation of tapentadol. The exact mechanism of action for tapentadol is unknown; however, preclinical studies have shown that tapentadol is a  $\mu$  opioid receptor agonist and a norepinephrine reuptake inhibitor.<sup>1</sup> Stimulation of the  $\mu$  opioid receptors results in analgesia, decreased gastrointestinal motility, euphoria, physical dependence, respiratory depression and sedation.<sup>3</sup> Norepinephrine reuptake inhibition is thought to provide analgesia as a result of norepinephrine mediated activation of spinal  $\alpha$ 2-adrenergic receptors, resulting in inhibition of presynaptic and postsynaptic nociceptive transmission.<sup>4</sup> Nucynta ER<sup>®</sup> (tapentadol extended-release) tablets are formulated to resist breaking and crushing; however, tablets may be flattened with a hammer and over half of the tapentadol may be extracted from a flattened tablet by use of an organic solvent with vigorous shaking over an extended period of time.<sup>2,13</sup>

**Table 1. Long-Acting Opioid Availability<sup>17</sup>**

Generic Name (Trade name)	Abuse Deterrent Formulation Available	Commercially Available
Buprenorphine (Belbuca <sup>®</sup> , Butrans <sup>®</sup> )	-	✓
Fentanyl (Duragesic <sup>®</sup> )	-	✓
Hydrocodone (Hysingla ER <sup>®</sup> )	✓	✓
Hydrocodone (Zohydro ER <sup>®</sup> )	-	✓
Hydromorphone (Exalgo <sup>®</sup> )	-	✓
Levorphanol (Levo-Dromoran <sup>®</sup> )	-	✓
Methadone (Diskets Dispersible <sup>®</sup> , Dolophine <sup>®</sup> , Methadose <sup>®</sup> , Methadone Intensol <sup>®</sup> )	-	✓
Morphine sulfate (Avinza <sup>®</sup> , Kadian <sup>®</sup> , MS Contin <sup>®</sup> )	-	✓
Morphine sulfate (MorphaBond <sup>®</sup> )	✓	-
Morphine sulfate/naltrexone (Embeda <sup>®</sup> )	✓	✓
Oxycodone (OxyContin <sup>®</sup> )	✓	✓
Oxycodone (Xtampza ER <sup>®</sup> )*	✓	-
Oxycodone/naloxone (Targiniq ER <sup>®</sup> )	✓	-
Oxymorphone (Opana <sup>®</sup> ER)	-	✓
Tapentadol (Nucynta ER <sup>®</sup> )	-	✓

\*Xtampza ER approval is tentative, pending patent litigation

**Therapeutic Indications/Efficacy**

Nucynta ER<sup>®</sup> (tapentadol extended-release) is FDA-approved for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. In addition, Nucynta ER<sup>®</sup> (tapentadol extended-release) is FDA-approved for neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.<sup>1</sup> FDA-approval of Nucynta ER<sup>®</sup> (tapentadol extended-release) for chronic pain was based upon the results of two phase III clinical trials that evaluated the safety and efficacy of Nucynta ER<sup>®</sup> (tapentadol extended-release) in chronic low back pain (LBP) and osteoarthritis (OA) of the knee.<sup>5,6</sup> FDA-approval of Nucynta ER<sup>®</sup> (tapentadol extended-release) for DPN was based upon the results of two phase III clinical trials in adult patients with DPN.<sup>7,8</sup> Nucynta ER<sup>®</sup> (tapentadol extended-release) has been evaluated for long-term safety and tolerability in two long-term extension studies, and for chronic cancer pain in two phase III clinical trials.<sup>9-12</sup>

The LBP study was a randomized, double-blind, multicenter, active and placebo-controlled trial performed in 981 patients aged 18 years or older with at least three months of non-malignant LBP. Patients were

randomized in a 1:1:1 fashion to Nucynta ER® (tapentadol extended-release) 100 mg to 250 mg twice daily (n=321), oxycodone ER 20 mg to 50 mg twice daily (n=334) or placebo (n=326). The trial was 15 weeks in length, consisting of a three week titration period and a 12-week maintenance period. Follow-up was conducted four days after the end of the 12-week maintenance period. The primary endpoint evaluated was change in average pain intensity from baseline to week 12 of the maintenance period. Treatment with Nucynta ER® (tapentadol extended-release) significantly reduced average pain intensity from baseline to week 12 of the maintenance period compared to placebo with a least squares mean difference (LSMD) of -0.8 (95% confidence interval [CI], -1.22 to -0.47; P<0.001). Secondary endpoints evaluated include change in average pain intensity from baseline to week 12 over the entire maintenance period, the proportion of patients that responded with ≥ 30% and ≥ 50% reduction in pain intensity at week 12 of the maintenance period, patient's global impression of change (PGIC) scores, Brief Pain Inventory (BPI) questionnaire scores, Short Form-36 (SF-36) scores, EuroQol-5 Dimension (EQ-5D) scores and sleep questionnaire scores.<sup>5</sup>

The OA study was a randomized, double-blind, multicenter, active and placebo-controlled trial performed in 1,023 patients aged 40 years and older with OA of the knee requiring the use of analgesics for at least three months. Patients were randomized in a 1:1:1 fashion to Nucynta ER® (tapentadol extended-release) 100 mg to 250 mg twice daily (n=344), oxycodone ER 20 mg to 50 mg twice daily (n=342) or placebo (n=337). The trial was 15 weeks in length, consisting of a three week titration period and a 12-week maintenance period, excluding screening and washout periods prior to randomization. Follow-up was conducted 14 days after the last dose of study medication. The primary endpoint evaluated was change in average pain intensity from baseline to week 12. Treatment with Nucynta ER® (tapentadol extended-release) significantly reduced average pain intensity from baseline to week 12 of the maintenance period compared to placebo with a LSMD of -0.7 (95% CI, -1.04 to -0.33). Secondary endpoints evaluated include change in average pain intensity from baseline to week 12 over the entire maintenance period, the proportion of patients that responded with ≥ 30% and ≥ 50% reduction in pain intensity at week 12 of the maintenance period, changes from baseline in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores, Patient Assessment of Constipation Symptoms (PAC-SYM) scores, EQ-5D scores and SF-36 scores.<sup>6</sup>

DPN Study 1 was a randomized, double-blind, placebo-controlled trial performed in 588 patients aged 18 years or older with painful DPN for at least six months. The trial was 15 weeks in length, consisting of a three week, open-label titration phase where all patients were titrated to their optimal Nucynta ER® (tapentadol extended-release) dose and a 12-week double-blind maintenance phase. After the titration phase, 389 patients were randomized in a 1:1 fashion to their optimal Nucynta ER® (tapentadol extended-release) dose (n=196) or placebo (n=193). The rate of patients completing the study was less than 70% in both Nucynta ER® (tapentadol extended-release) treated and placebo groups. The primary endpoint evaluated was the change from baseline in average pain intensity over the last week of the study. For the primary endpoint, the LSMD between Nucynta ER® (tapentadol extended-release) and placebo was -1.3 (95% CI, -1.70 to -0.92, P<0.001). Of note, the least squares mean change in average pain intensity from baseline was 0.0 in the Nucynta ER® (tapentadol extended-release) group. This indicates no change in average pain intensity from baseline for the Nucynta ER® (tapentadol extended-release) group, and worsening average pain intensity for placebo at the end of the study. Secondary endpoints evaluated include the proportion of patients that responded with ≥ 30% and ≥ 50% reduction in pain intensity at week 12 of the maintenance period and PGIC at weeks 2, 6 and 12 of the maintenance period.<sup>7</sup>

DPN Study 2 was a randomized, double-blind, placebo-controlled trial performed in 459 patients aged 18 years or older with painful DPN for at least six months. The trial was 15 weeks in length, consisting of a three week, open-label titration phase where all patients were titrated to their optimal Nucynta ER® (tapentadol extended-release) dose and a 12-week double-blind treatment phase. After the titration phase, 338 patients were randomized in approximately a 1:1 fashion to their optimal Nucynta ER® (tapentadol extended-release) dose (n=166) or placebo (n=152). The rate of patients completing the study was less than 80% in both Nucynta ER® (tapentadol extended-release) treated and placebo groups. For the primary endpoint, the LSMD between Nucynta ER® (tapentadol extended-release) and placebo

was -0.95 (95% CI, -1.42 to -0.49;  $P < 0.001$ ), in favor of treatment with Nucynta ER<sup>®</sup> (tapentadol extended-release). Of note, the mean (SD) change from baseline to week 12 of the double-blind treatment phase for Nucynta ER<sup>®</sup> (tapentadol extended-release) was 0.28 (2.04), indicating that pain worsened over the course of treatment, but to a lesser extent than with placebo (1.30[2.43]). Secondary endpoints evaluated include the proportion of patients that responded with  $\geq 30\%$  and  $\geq 50\%$  reduction in pain intensity at week 12 of the double-blind treatment phase, PGIC at the end of the double-blind treatment phase and changes from baseline to the end of the double-blind treatment phase on the BPI-SF, Neuropathic Pain Symptom Inventory (NPSI), SF-36 and EQ-5D.<sup>8</sup>

An open-label, active-controlled, long-term study assessed the safety and tolerability of treatment with Nucynta ER<sup>®</sup> (tapentadol extended-release) in patients aged 18 years or older with chronic LBP or OA of the hip or knee. The study was 52 weeks in length, consisting of a one week titration period and a 51-week maintenance period. Patients were randomized in a 4:1 fashion to receive treatment with either Nucynta ER<sup>®</sup> (tapentadol extended-release) ( $n=894$ ) or oxycodone ER ( $n=223$ ). The percentage of patients that completed the study was 46.2% for Nucynta ER<sup>®</sup> (tapentadol extended-release) and 35.0% for oxycodone ER. The most common reason for discontinuing study medication was adverse events in both the Nucynta ER<sup>®</sup> (tapentadol extended-release) and oxycodone ER groups with 22.7% and 36.8% of patients discontinuing treatment, respectively. The time to discontinuing treatment was significantly longer for Nucynta ER<sup>®</sup> (tapentadol extended-release) compared to oxycodone ER ( $P < 0.001$ ). The incidence of treatment emergent adverse events that lead to study discontinuation was lower in the Nucynta ER<sup>®</sup> (tapentadol extended-release) group compared to the oxycodone ER group for nausea, constipation, dizziness, vomiting, fatigue, somnolence and pruritus. A lower proportion of patients discontinued treatment due to lack of efficacy in the oxycodone ER group compared to the Nucynta ER<sup>®</sup> (tapentadol extended-release) group (3.1% compared to 8.1%, respectively). There were no deaths reported during the study.<sup>9</sup> A one year extension study of the long-term safety and tolerability study, the LBP study and the OA study in 1,154 patients revealed comparable results, and authors concluded that Nucynta ER<sup>®</sup> (tapentadol extended-release) was well tolerated and effective for chronic OA or LBP over up to two years of treatment.<sup>10</sup>

A randomized, double-blind, multicenter, active-controlled, phase III clinical trial evaluated the safety and efficacy of Nucynta ER<sup>®</sup> (tapentadol extended-release) compared to oxycodone ER in 343 patients aged 20 years or older with chronic cancer-related pain (CCP). The trial was four weeks in length, excluding one week screening and post-treatment periods. Patients were randomized in a 1:1 fashion to receive treatment with either Nucynta ER<sup>®</sup> (tapentadol extended-release) dosed 25 mg to 200 mg twice daily ( $n=168$ ) or oxycodone ER 5 mg to 40 mg twice daily ( $n=172$ ). The primary endpoint evaluated was mean change in average pain intensity from baseline to the last three days of study drug administration. Per protocol analysis was used for all efficacy endpoints. For the primary endpoint, the LSMD between Nucynta ER<sup>®</sup> (tapentadol extended-release) and oxycodone ER was -0.06 (95% CI, -0.506 to 0.383), indicating treatment with Nucynta ER<sup>®</sup> (tapentadol extended-release) was non-inferior to oxycodone ER. Secondary endpoints evaluated include the proportion of patients that responded with  $\geq 30\%$  and  $\geq 50\%$  reduction in pain intensity from baseline during the last three days of treatment, PGIC and rescue medication used.<sup>11</sup> In addition to this CCP study, results of an open-label trial in CCP patients suggest that conversion from morphine ER to Nucynta ER<sup>®</sup> (tapentadol extended-release) is relatively safe and effective with improved gastrointestinal tolerability for Nucynta ER<sup>®</sup> (tapentadol extended-release) compared to morphine ER.<sup>12</sup>

Nucynta ER<sup>®</sup> (tapentadol extended-release) is not approved as an abuse-deterrent formulation (ADF) by the FDA; however, *in vitro* laboratory manipulation studies and clinical abuse potential studies have been performed.<sup>1,2,13,14</sup> An *in vitro* laboratory manipulation study revealed that Nucynta ER<sup>®</sup> (tapentadol extended-release) tablets were not able to be deformed by using two metal spoons, pill crusher use resulted in minimal deformation, use of a standard pharmacopeia breaking force tester resulted in slight deformation and use of a hammer flattened tablets without pulverization or breakage. Tablets tampered with spoons, a pill crusher and breaking force tester were found to have similar release profiles; however, tablets flattened by hammering released tapentadol faster with 30% of tapentadol released after 30

minutes. Similarly, intact tablets resisted extraction in solvents, but tablets flattened by hammering allowed for > 50% of tapentadol to be released over an extended period of time with vigorous shaking. The *in vitro* manipulation study did not mention any attempt to tamper with the tablets via use of a grinding apparatus.<sup>13</sup>

Two clinical abuse potential studies were conducted in 25 volunteers that abused oxycodone ER intranasally or intravenously prior to study enrollment. Study 1 evaluated intranasal abuse and Study 2 evaluated intravenous abuse. Subjects were given approved tools including hammers, razors, lighters, spoons, dollar bills, syringes, cotton and water to use to prepare doses of the study medications. In Study 1, the primary endpoint evaluated was willingness to insufflate the powder made. For the oxycodone ER 40 mg tablet, 100% of subjects were willing to insufflate the powder they made compared to 24% and 16% for Nucynta ER<sup>®</sup> (tapentadol extended-release) 50 mg and 250 mg tablets, respectively. The primary endpoint evaluated in Study 2 was the percent yield of active drug in solution the subjects were able to extract. The mean (SD) percent yield of oxycodone ER 40 mg tablet was significantly higher with 37.02% (16.67%) extracted compared to 3.52% (2.77%) for Nucynta ER<sup>®</sup> (tapentadol extended-release) 50 mg tablets (P=0.008). None of the subjects were able to extract tapentadol from the Nucynta ER<sup>®</sup> (tapentadol extended-release) 250 mg tablet as a liquid. Both Study 1 and Study 2 indicated that subjects spent more time tampering with Nucynta ER<sup>®</sup> (tapentadol extended-release) tablets than oxycodone ER tablets. Of note, the comparator oxycodone ER tablets were not the reformulated oxycodone ER that is currently approved as an ADF.<sup>14</sup>



**Table 2. Clinical Trials**<sup>5-8,11,14</sup>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Buynak et al<sup>5</sup></p> <p>Tapentadol ER 100 mg BID</p> <p>vs</p> <p>oxycodone CR 20 mg BID</p> <p>vs</p> <p>placebo</p> <p>Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for three days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID).</p> <p>APAP ≤1,000 mg/day (max of three consecutive days) was permitted.</p>	<p>AC, DB, MC, PC, PRO, RCT</p> <p>Patients ≥18 years with a history of non-malignant low back pain for ≥3 months who were dissatisfied with their current treatment, had a baseline pain intensity ≥5 on an 11-point rating scale after washout, and whose previous opioid daily doses, if applicable, were equivalent to ≤160 mg of oral morphine</p>	<p>N=981</p> <p>12 weeks (maintenance phase after a 3-week titration phase)</p>	<p>Primary:</p> <p>Change from baseline in mean pain intensity at week-12 of the maintenance period</p> <p>Secondary:</p> <p>Change from baseline in mean pain intensity over the entire 12-week maintenance period, proportion of patients with ≥30 and ≥50% reduction in pain intensity at week-12 of maintenance, PGIC score, BPI survey, SF-36 health survey</p>	<p>Primary:</p> <p>Throughout the 12-week maintenance period, average pain intensity scores improved in both the tapentadol ER and oxycodone CR groups relative to placebo.</p> <p>The mean (SD) change in pain intensity from baseline to week 12 was -2.9 (2.66) for tapentadol ER and -2.1 (2.33) for placebo resulting in a least square mean difference vs placebo of -0.8 (95% CI, -1.22 to -0.47; P&lt;0.001).</p> <p>The mean change in pain intensity from baseline over the entire maintenance period was -2.8 (2.50) for tapentadol ER and -2.1 (2.20) for placebo, corresponding to a least square mean difference vs placebo of -0.7 (95% CI, -1.06 to -0.35; P&lt;0.001).</p> <p>Secondary:</p> <p>The mean pain intensity was also reduced for the oxycodone CR group. Compared to the placebo group at week 12 the least square mean difference was -0.9 (95% CI, -1.24 to -0.49; P&lt;0.001); and over the entire maintenance period the least square mean difference was -0.8 (95% CI, -1.16 to -0.46; P&lt;0.001).</p> <p>Reductions in mean pain intensity were significantly greater with tapentadol ER than with placebo at week-12 of the maintenance period both for patients with moderate and severe baseline pain intensity. Significantly greater reductions in mean pain intensity with tapentadol ER compared to placebo were also observed for the overall maintenance period in patients with both moderate baseline pain intensity and severe baseline pain intensity.</p> <p>Reductions in mean pain intensity were also significantly greater with oxycodone CR than with placebo for patients with moderate and severe baseline pain intensity at both week 12 of the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>maintenance period and for the overall maintenance period.</p> <p>The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol ER group and the placebo group (<math>P=0.004</math>), with a higher percentage of patients showing improvements in pain scores in the tapentadol ER group than in the placebo group. The overall distribution of responders at week 12 in the oxycodone CR group, however, was not significantly different from the placebo group (<math>P=0.090</math>).</p> <p>A total of 39.7% of patients treated with tapentadol ER compared to 27.1% of patients treated with placebo responded with <math>\geq 30\%</math> improvement in pain intensity at week-12 compared to baseline (<math>P&lt;0.001</math>).</p> <p>A total of 27.0% of patients treated with tapentadol ER compared to 18.9% of patients treated with placebo responded with 50% improvement in pain intensity at week-12 compared to baseline (<math>P&lt;0.016</math>).</p> <p>The percentage of patients in the oxycodone CR group with <math>\geq 30\%</math> improvement in pain intensity at week-12 compared to baseline was 30.4% (<math>P=0.365</math>) and did not differ significantly from placebo (percent among placebo group not reported). Conversely, the percentage of patients in the oxycodone CR group with <math>\geq 50\%</math> improvement in pain intensity at week-12 compared to baseline was 23.3% (<math>P=0.174</math>) and did not differ significantly from placebo (percent among placebo group not reported).</p> <p>At endpoint, there was a significant difference in PGIC ratings for both tapentadol ER (<math>P&lt;0.001</math>) and oxycodone CR (<math>P&lt;0.001</math>) compared to placebo.</p>



Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Compared to placebo, both tapentadol ER and oxycodone CR showed significant reductions from baseline to week-12 in the BPI total score, the pain interference subscale score, and the pain subscale score.</p> <p>The percentage of patients with “any pain today other than everyday kinds of pain” on the BPI survey at baseline was 88.6, 85.6, and 86.1% for the placebo group, tapentadol ER group, and oxycodone CR group, respectively.</p> <p>At week 12, the percentage scores decreased to 80.7% for the placebo group, 69.8% for the tapentadol ER group, and 67.3% for the oxycodone CR group.</p> <p>The percentage of patients who reported “at least 50% pain relief during the past week” was similar for all three treatment groups at baseline for the placebo, tapentadol ER, and oxycodone ER groups (23.4, 24.7, and 20.9%, respectively). These results increased to 59.7, 75.4, and 80.0% among the placebo, tapentadol ER, and oxycodone CR groups, respectively at week 12.</p> <p>Treatment with both tapentadol ER and oxycodone CR significantly improved physical health status compared to placebo, as reflected by the physical component summary score.</p> <p>The mean changes at week-12 from baseline on the SF-36 survey for four of eight measures (physical functioning, role-physical, bodily pain, and vitality) were significantly improved in the tapentadol ER group compared to the placebo group.</p> <p>The mean changes from baseline were significantly improved for role-physical and bodily pain scores among the oxycodone CR group compared to the placebo group.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>No clinically important changes in laboratory values, vital signs, or electrocardiogram findings were attributed to treatment. Overall, at least one adverse event was reported by 59.6, 75.5, and 84.8% of patients in the placebo, tapentadol ER, and oxycodone CR groups, respectively.</p> <p>The most commonly reported events (reported by &gt;10% in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence, the majority of which were categorized as mild to moderate in intensity across all treatment groups.</p> <p>In the oxycodone CR group, the incidence of vomiting, constipation, and pruritus was nearly double incidence in the tapentadol ER group.</p>
<p>Afilalo et al<sup>6</sup></p> <p>Tapentadol ER 100 mg BID</p> <p>vs</p> <p>placebo</p> <p>vs</p> <p>oxycodone CR 20 mg BID</p> <p>Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for three days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg</p>	<p>AC, DB, MC, PC, RCT</p> <p>Patients ≥40 years of age with a diagnosis of OA of the knee (per ACR criteria)</p> <p>functional capacity class I-III, and pain at reference joint requiring analgesics (both non-opioid and opioid doses ≤ 160 mg oral morphine daily) for ≥3 months,</p>	<p>N=1,030</p> <p>12 weeks (maintenance phase after a 3-week titration phase)</p>	<p>Primary: Change in average pain intensity at week-12 of the maintenance period compared to baseline</p> <p>Secondary: Change in average pain intensity over the entire 12-week maintenance period compared to baseline</p>	<p>Primary: Significant pain relief was achieved with tapentadol ER vs placebo at study endpoint. The least square mean difference was -0.7 (95% CI, -1.04, -0.33) at week 12 of the maintenance period compared to placebo.</p> <p>Secondary: The least square mean difference was -0.7 (95% CI, -1.00 to -0.33) for the overall maintenance period for tapentadol compared to placebo (P-values not reported).</p> <p>The average pain intensity rating with oxycodone CR was reduced significantly compared to placebo from baseline for the overall maintenance period (least square mean difference vs placebo, -0.3; 95% CI, -0.67 to 0.00), but was not statistically significantly lower at week-12 of the maintenance period (-0.3; 95% CI, -0.68 to 0.02); P-values not reported.</p> <p>The percentage of patients who achieved ≥30% reduction from baseline in average pain intensity at week-12 of the maintenance</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID).</p> <p>APAP ≤1,000 mg/day (max of three consecutive days) was permitted.</p>	<p>who were dissatisfied with their current analgesic regimen, and had a baseline pain intensity score ≥5 during the three days prior to randomization</p>			<p>period was not significantly different between tapentadol ER and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; P=0.002).</p> <p>Treatment with tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week-12 of the maintenance period vs treatment with placebo (32.0 vs 24.3%; P=0.027). Conversely, treatment with oxycodone CR resulted in a significantly lower percentage of patients achieving at least a 50% reduction in average pain intensity from baseline at week-12 of the maintenance period vs treatment with placebo (17.3 vs 24.3%; P=0.023).</p> <p>Tapentadol ER was significantly better than placebo at week-12 on the WOMAC global scale with a least square mean difference of -0.21 (95% CI, -0.357 to -0.065; P=0.0047) compared to the least square mean difference between oxycodone CR and placebo -0.18 (95% CI, -0.343 to -0.010; P=0.0381).</p> <p>The pain subscale for tapentadol ER compared to placebo was a least square mean difference of -0.27 (95% CI, -0.422 to -0.126; P&lt;0.001) compared to the least square mean difference between oxycodone CR and placebo of -0.17 (95% CI, -0.338 to -0.000; P=0.051).</p> <p>The physical function subscale at week-12 was significantly improved with tapentadol ER and placebo (least square mean difference of -0.21; 95% CI, -0.357 to -0.060; P=0.006), whereas the least square mean difference between oxycodone CR and placebo was -0.20 (95% CI, -0.373 to -0.034; P=0.019).</p> <p>The stiffness subscale assessment was improved with tapentadol ER compared to placebo with a least square mean difference of -0.17 (95% CI, -0.377 to -0.002; P=0.053); however the difference</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>was not statistically significant. Conversely, the least square mean difference between oxycodone ER and placebo was -0.10 (95% CI, -0.292 to 0.096; P=0.321), which also was not statistically significant.</p> <p>The incidence of adverse events was 61.1% with placebo, 75.9% with tapentadol ER, and 87.4% with oxycodone CR. The most common events (≥10% in any group) in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The majority of reported events were mild to moderate in severity. Events leading to discontinuation occurred in 6.5% of patients treated with placebo, 19.2% of patients treated with tapentadol ER, and 42.7% of patients treated with oxycodone ER. Gastrointestinal-related events were the most common events in both active treatment groups.</p>
<p>Schwartz et al<sup>7</sup></p> <p>Tapentadol ER 100 to 250 mg BID (fixed, optimal dose identified for patients during OL phase of trial)</p> <p>vs</p> <p>placebo</p> <p>Initial treatment with tapentadol ER 50 mg BID for three days; then titrated to tapentadol ER 100 mg BID for three days (minimum study dose for maintenance); subsequent titration in 50 mg</p>	<p>DB, PC, PG, RCT</p> <p>Adults ≥18 years with Type 1 or 2 DM and painful peripheral neuropathy for ≥6 months with a history of analgesic use for diabetic peripheral neuropathy and dissatisfaction with current treatment (opioid daily doses</p>	<p>N=395 (A total of 588 received study drug through OL titration phase; a total of 395 were randomized to DB phase of the study)</p> <p>12 weeks (maintenance phase after a 3-week titration phase)</p>	<p>Primary: The change from baseline in average pain intensity over the last week (week-12) of the maintenance phase</p> <p>Secondary: Proportion of patients with improvements in pain intensity of at least 30 and 50% at week 12 (i.e., responder rate), PGIC at</p>	<p>Primary: The least square mean change in average pain intensity from the start of DB treatment to week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol ER group, indicating no change in pain intensity. The least square mean difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; P&lt;0.001).</p> <p>Secondary: The mean changes in average pain intensity scores (on 11-point rating scale) from baseline to week-12 were similar between males and females who received tapentadol ER, for those &lt;65 years of age and those &gt;65 years who received tapentadol ER, as well as those who were opioid-naïve and opioid-experienced.</p> <p>From pre-titration to week 12 of maintenance treatment, at least a 30% improvement in pain intensity was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients (P=0.017).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>increments every three days (within dose range of 100 to 250 mg BID).</p> <p>APAP ≤2,000 mg/day was permitted during the OL phase, except during the last four days.</p>	<p>equivalent to &lt; 160 mg of oral morphine), an average pain intensity score ≥5 on an 11-point rating scale, and effective method of birth control (if applicable)</p>		<p>weeks two, six, and 12, and safety measures</p>	<p>At least a 50% improvement in pain intensity from pre-titration to week-12 was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients.</p> <p>There was a statistically significant difference in the distribution of responder rates for patients with any degree of improvement (pre-titration to week-12) between the tapentadol ER and placebo groups (P=0.032).</p> <p>Of the patients who achieved ≥ 30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER treatment, 60.8% maintained ≥30% improvement through week 12 (maintenance phase); whereas 34.0% of patients who had not achieved at least a 30% improvement in pain intensity (titration phase) and were randomized to tapentadol ER reached ≥30% improvement from pre-titration by week 12 of the maintenance period.</p> <p>Of those patients who were randomized to placebo after achieving ≥30% improvement in pain intensity (titration phase), 48.7% of patients maintained ≥30% improvement through the maintenance phase, while only 17.5% of patients who were randomized to placebo and had not reached ≥30% improvement (titration phase) achieved ≥30% improvement in pain intensity during the maintenance phase.</p> <p>Among patients who achieved ≥50% improvement in pain intensity (titration phase) and were randomized to treatment with tapentadol ER, 59.1% of patients maintained ≥50% improvement through week 12 (maintenance phase); whereas 18.0% of patients who had not achieved ≥50% improvement (titration phase) and were randomized to tapentadol ER reached ≥50% improvement from pre-titration by week 12 of the maintenance period.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Among patients who were randomized to placebo after achieving <math>\geq 50\%</math> improvement in pain intensity (titration phase), 36.4% of patients maintained <math>\geq 50\%</math> improvement through the maintenance phase, while only 16.5% of those randomized to placebo and had not reached <math>\geq 50\%</math> improvement during titration reached <math>\geq 50\%</math> improvement during the maintenance phase.</p> <p>A total of 64.4% of tapentadol ER-treated patients and 38.4% of placebo-treated patients reported on the PGIC scale that their overall status was “very much improved” or “much improved” (<math>P &lt; 0.001</math>).</p> <p>The overall incidence of adverse events (maintenance phase) was 70.9% among the tapentadol ER group and 51.8% among the placebo group. The most commonly reported events among the active treatment group were nausea, anxiety, diarrhea, and dizziness.</p> <p>During the maintenance phase, the overall incidence of adverse events was similar between males and females, those ages <math>&lt; 65</math> years and <math>&gt; 65</math> years, and among opioid-naïve and opioid-experienced individuals who received tapentadol ER.</p> <p>Treatment-emergent serious adverse events occurred in 1.4% of tapentadol ER-treated patients in the titration phase; and among 5.1% of the tapentadol ER-treated patients and 1.6% of placebo-treated patients in the maintenance phase.</p>
<p>Vinik et al<sup>8</sup></p> <p>Tapentadol ER 100 to 250 mg BID</p> <p>vs</p>	<p>DB, PG, RCT</p> <p>Patients <math>\geq 18</math> years of age with type 1 or 2 DM and chronic (<math>\geq 6</math> months)</p>	<p>N=358</p> <p>12 weeks</p>	<p>Primary:</p> <p>Mean change in average pain intensity from the start to week 12</p> <p>Secondary:</p>	<p>Primary:</p> <p>The mean change in pain intensity (LOCF) from start of double-blind treatment to week 12 was as follows: placebo, 1.30; tapentadol ER, 0.28 (2.04; least squares mean difference, <math>-0.95</math>; 95% CI, <math>-1.42</math> to <math>-0.49</math>; <math>P &lt; 0.001</math>).</p> <p>From pre-titration to the last week of treatment, <math>\geq 30\%</math></p>



Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>Patients were titrated up to a dose of tapentadol ER 100 to 250 mg BID during a three-week OL period. Those with <math>\geq 1</math> point reduction in pain intensity (on 11 point scale) entered the randomized phase.</p> <p>The use of any analgesic except study drug or permitted rescue medication was prohibited throughout the study. Neuroleptics, SNRI, anticonvulsants, and antiparkinsonian drugs were prohibited during the study and within 14 days before screening because their use could confound the primary assessment of analgesic efficacy. Use of SSRI was allowed if patients were on a stable dose for <math>\geq 3</math> months before screening.</p>	<p>moderate to severe DPN pain despite optimized diabetic regimen for <math>\geq 3</math> months and analgesic use for <math>\geq 3</math> months</p>		<p>Proportions of patients with <math>\geq 30</math> and <math>\geq 50\%</math> improvement in pain intensity, PGIC and changes in BPI and BPI-SF, pain interference and pain intensity subscale scores, subscales of the NPSI, SF-36 Health Survey subscales and summary Scale, EuroQol 5-Dimension health status index and safety</p>	<p>improvement in pain intensity was observed in 45.4% (69/152) of patients in the placebo group and 55.4% (92/166) of patients in the tapentadol ER group (<math>P=0.032</math>).</p> <p>At least a 50% improvement was observed in 28.9% (44/152) of patients in the placebo group and 40.4% (67/166) of patients in the tapentadol ER group (<math>P=0.015</math>).</p> <p>The distribution of PGIC scores was significantly different at the end point between treatment groups (<math>P&lt;0.001</math>); 45.3% (63/139) of patients in the placebo group reported their PGIC status as “very much improved” or “much improved” compared with 66.0% (99/150) of patients in the tapentadol ER group.</p> <p>Mean (SD) BPI-SF pain interference scores worsened in the placebo group and improved in the tapentadol ER group (<math>P=0.003</math> favoring tapentadol ER); mean (SD) BPI-SF pain intensity subscale scores increased in the placebo group and to a lesser extent in the tapentadol ER group (<math>P&lt;0.001</math> favoring tapentadol ER).</p> <p>Statistically significant differences in changes from the start of double-blind maintenance were observed between tapentadol ER and placebo for all NPSI subscales and the total score (<math>P\leq 0.015</math> for all scores, favoring tapentadol ER).</p> <p>Significant differences in mean changes from start of the double-blind phase to end point of the double-blind maintenance phase were observed between the tapentadol ER and placebo groups in favor of tapentadol ER in the SF-36 role-physical and bodily pain subscale scores and the physical component summary score (<math>P\leq 0.004</math> for all).</p> <p>A significant difference was observed between the tapentadol ER and placebo groups in favor of tapentadol ER in the mean (SD)</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>change from the start of double-blind treatment (mean [SD] score at start: placebo, 0.71 [0.16]; tapentadol ER, 0.70 [0.14]) to double-blind end point in the EQ-5D health status index (mean [SD] change: placebo, 20.10 [0.26]; tapentadol ER, 0.00 [0.20; least squares mean difference for tapentadol ER minus placebo, 0.10 (95% CI 0.05 to 0.15); P&lt;0.001]).</p> <p>Secondary: Treatment-emergent adverse events (≥10%) in the tapentadol ER group during the double-blind maintenance phase were nausea (21.1%) and vomiting (12.7%).</p>
<p>Imanaka et al<sup>11</sup></p> <p>Tapentadol ER 100 to 500 mg daily</p> <p>vs</p> <p>morphine SR 20 to 140 mg daily</p> <p>Starting doses were calculated based upon conversion from previous opioid therapy. Doses could be titrated based upon response to therapy throughout the OL period.</p> <p>Patients were allowed to use oral morphine IR or oxycodone IR as rescue medication for breakthrough pain. The dose per intake of rescue</p>	<p>MC, OL, PG, RCT</p> <p>Patients ≥20 years of age receiving around-the-clock strong opioid therapy for moderate to severe, chronic malignant tumor-related cancer pain and had a mean pain intensity score &lt;4 during the three days prior to randomization</p>	<p>N=100</p> <p>8 weeks</p>	<p>Primary: Proportion of patients who maintained pain control during the first week of open-label treatment*</p> <p>Secondary: Average weekly pain intensity scores, PGIC and safety evaluations</p>	<p>Primary: In the tapentadol ER group (n = 50), 84.0 % of patients (42/50; 95 % CI, 70.89 to 92.83) maintained pain control during week one.</p> <p>Secondary: After switching from previous opioid analgesics to tapentadol ER, mean average weekly pain intensity scores were ≤2 during the entire eight-week treatment period. Mean changes from baseline in average pain intensity were ≤0.4 throughout the treatment period.</p> <p>On the PGIC, 2.1 % (1/48), 2.1 % (1/48), 22.9 % (11/48), and 50.0 % (24/48) of patients in the tapentadol ER group reported that their overall condition was “very much improved,” “much improved,” “minimally improved,” and “not changed,” respectively, at week one compared with 0 %, 10.7 % (3/28), 28.6 % (8/28), and 53.6 % (15/28) reporting these ratings at week eight.</p> <p>Tapentadol ER was associated with a lower incidence of gastrointestinal treatment-emergent adverse events than morphine SR [38.0 % (19/50) vs. 54.0 % (27/50)], including constipation [12.0 % (6/50) vs. 20.0 % (10/50)] and vomiting [6.0</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
medication must have been no more than one sixth of the total daily dose of the around-the-clock opioid analgesic.				% (3/50) vs. 26.0 % (13/50)].
<p>Vosburg et al<sup>14</sup></p> <p>Tapentadol ER 50 mg tablets</p> <p>vs</p> <p>tapentadol ER 250 mg tablets</p> <p>vs</p> <p>oxycodone ER 40 mg tablets</p> <p>Tools that had been specifically requested by the participant for preparing the tablets for abuse were provided. Participants were able to tamper with the tablets for up to an hour to turn them into a form suitable for snorting (Study 1) or shooting (Study 2).</p>	<p>SB, Randomized, repeat measures study</p> <p>Patients between 21 and 60 years of age currently abusing oxycodone IR or ER intranasally (Study 1) or intravenously (Study 2)</p>	<p>N=25 (Study 1) N=25 (Study 2)</p> <p>Single encounter</p>	<p>Primary: Percentage of participants who indicated they would snort the tampered tablets (Study 1); Percent yield of active drug in solution (Study 2)</p> <p>Secondary: Time spent tampering with the tablets (Study 1 and 2); particle size distribution of the tampered tablets and the self-reported maximum time participants willing to spend on a routine basis preparing the tablets for intranasal abuse (Study 1); self-</p>	<p>Primary: Tampered tapentadol tablets were less desirable than the tampered oxycodone tablets. Few individuals were willing to snort the tapentadol particles (tapentadol ER 50 mg: 24%, tapentadol ER 250 mg: 16%; oxycodone ER 40 mg: 100% P&lt;.001) There were no statistically significant differences between the percentages of participants who were willing to snort the two tapentadol groups. (Study 1).</p> <p>There was less drug extracted from the tapentadol ER 50 mg tablet than from the oxycodone ER 40 mg tablet (3.5% vs. 37.0%, P=0.008), and no samples from the tapentadol ER 250 mg tablets contained analyzable solutions of the drug (Study 2).</p> <p>Secondary: It took participants longer to tamper with the tapentadol formulations (Study 1: tapentadol ER 50 mg: 5.9 minutes vs oxycodone ER 40 mg: 2.9 minutes, P&lt;0.01; tapentadol ER 250 mg: 7.1 minutes vs oxycodone ER 40 mg: 2.9 minutes, P&lt;0.01; Study 2: tapentadol ER 250 mg: 10.58 minutes vs oxycodone ER 40 mg: 6.57 minutes, P&lt;0.05).</p> <p>Lower percentages of the initial, intact tablet by weight were recovered as tampering products from the oxycodone ER 40 mg tablets than from the tapentadol groups. This was likely due to the fine powder produced from the oxycodone ER 40 mg during the crushing process which stuck to the work surface or potentially blew away during the product transfer (Study 1).</p> <p>Participants also reported that they were willing to spend more</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			reported willingness to inject the tampered product and self-reported maximum time participants would be willing to spend on a routine basis preparing the tablets for abuse	<p>time preparing tapentadol 50 mg and 250 mg tablets than oxycodone ER 40 mg tablets. (11.6 minutes vs 4.8 minutes, <math>P&lt;0.01</math>; 10.8 minutes vs 4.8 minutes, <math>P&lt;0.05</math>, respectively) (Study 1).</p> <p>There were no differences between the tapentadol 50 mg and 250 mg compared to the oxycodone ER 40 mg among the maximum amounts of time that participants would be willing to spend preparing tablets for intravenous use (17.67 minutes and 22.52 minutes vs 15.22 minutes; <math>P</math> value not reported). (Study 2)</p> <p>All participants were willing to inject the oxycodone ER 40 mg (100%), yet few were willing to inject the tapentadol ER 50 solution (16%), and none were willing to inject the tapentadol ER 250 solution (0%). (Study 2)</p>

\*In this study, maintenance of pain control was defined as those patients who change from baseline on an 11 point numerical scale was  $<1.5$  points for three consecutive days and who had no more than two doses of rescue medication per day for three consecutive days

Drug regimen abbreviations: BID=twice daily

Study abbreviations: AC=Active Control, CI=confidence interval, DB=double-blind, MC=multicenter, , PC=placebo-controlled, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SD=standard deviation, SR=sustained-release,

Other abbreviations: ACR=American College of Rheumatology, APAP=acetaminophen, BPI= Brief Pain Inventory, BPI-SF= Brief Pain Inventory-Short Form, CR=controlled-release, DM=diabetes mellitus, ER=extended-release, IR=immediate-release, LOCF=last observation carried forward, NPSI=neuropathic pain symptom inventory, OA=osteoarthritis, PGIC=patient global impression of change, SF-36=Short Form-36, SNRI=serotonin norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor, WOMAC index=Western Ontario and McMaster Universities Index

**Pharmacokinetics/Pharmacogenomics<sup>1</sup>****Absorption**

The mean oral bioavailability of Nucynta ER® (tapentadol extended-release) is approximately 32% due to extensive first pass metabolism. The time to peak serum concentration ( $T_{max}$ ) of Nucynta ER® (tapentadol extended-release) is between three to six hours after administration. Increases in mean exposure (AUC) are proportional to increases in doses of Nucynta ER® (tapentadol extended-release) over the therapeutic dose range, and steady-state is reached after the third dose. When Nucynta ER® (tapentadol extended-release) was administered after a high-fat meal, the AUC and peak serum concentration ( $C_{max}$ ) increased by 6% and 17%, respectively. Nucynta ER® (tapentadol extended-release) may be administered with or without food. Administration of Nucynta ER® (tapentadol extended-release) with alcohol has been shown to increase mean  $C_{max}$  by 28% to 48% in healthy, fasted volunteers compared to controls.

**Distribution**

Nucynta ER® (tapentadol extended-release) is readily distributed throughout the body. The volume of distribution (VD) for tapentadol was 540 L  $\pm$  98 L following intravenous administration. Approximately 20% of tapentadol is bound to plasma protein. Due to the low level of plasma protein binding, clinically relevant drug interactions with Nucynta ER® (tapentadol extended-release) related to displacement from the plasma protein is unlikely.

**Metabolism**

The main metabolic pathways for the metabolism of Nucynta ER® (tapentadol extended-release) are Phase II conjugation pathways. Glucuronidation is the major Phase II metabolic pathway. Approximately 70% of the Nucynta ER® (tapentadol extended-release) dose is excreted into the urine in conjugated forms, with 55% as the O-glucuronide and 15% as sulfate of tapentadol. Phase II glucuronidation is considered a high capacity/low affinity system. As such, clinically relevant drug interactions via Phase II metabolism are not likely.

Nucynta ER® (tapentadol extended-release) is also metabolized to N-desmethyltapentadol by CYP2C9 and CYP2C19 and hydroxytapentadol by CYP2D6 for 13% and 2% of the dose, respectively. Considering the relatively low amount of Nucynta ER® (tapentadol extended-release) metabolized by CYP450, it is unlikely that clinically relevant drug interactions mediated by CYP450 enzymes occur. Overall, approximately 97% of a Nucynta ER® (tapentadol extended-release) dose is metabolized, and 3% is excreted unchanged in the urine.

**Excretion**

Nucynta ER® (tapentadol extended-release) is excreted via the kidneys as 99% of the dose. The total clearance of Nucynta ER® (tapentadol extended-release) is 1,603  $\pm$  227 mL/min. The mean terminal half-life is five hours after oral administration of Nucynta ER® (tapentadol extended-release).

**Table 3. Pharmacokinetics<sup>1</sup>**

Generic Name	$T_{max}$ (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Tapentadol	3 to 6	12	99	None	5

**Special Populations****Table 4. Special Populations<sup>1</sup>**

Population	Precaution
Elderly	Among the total number of individuals in clinical trials, only a small number were elderly, including 28% over the age of 65 years and 7% over the age of 75. No overall differences in effectiveness were observed between the elderly and younger individuals. The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower

	<p>mean C<sub>max</sub> observed in the elderly subject group compared to young adult subjects.</p> <p>Recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function; however, given the elderly are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses.</p>
Renal dysfunction	<p>Among individuals with mild (creatinine clearance [CrCl]: 50 to &lt; 80 mL/minute), moderate (CrCl: 30 to &lt;50 mL/minute), and severe (CrCl: &lt; 30mL/minute) renal impairment, the AUC of tapentadol-O-glucuronide was 1.5-, 2.5-, and 5.5-fold higher compared to those with normal renal function, respectively.</p> <p>The safety and effectiveness have not been established in patients with severe renal impairment (CrCl &lt;30mL/minute); therefore, the use of Nucynta<sup>®</sup> ER (tapentadol) in patients with severe renal impairment is not recommended due to accumulation of metabolite formed by glucuronidation of tapentadol.</p>
Hepatic dysfunction	<p>Tapentadol administration results in higher exposures and serum levels of tapentadol in individuals with impaired hepatic function compared to individuals with normal hepatic function.</p> <p>The ratio of tapentadol pharmacokinetic parameters for the mild hepatic impairment group (Child-Pugh Score 5 to 6) and moderate hepatic impairment group (Child-Pugh Score 7 to 9) compared to normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C<sub>max</sub>; and 1.2 and 1.4, respectively, for the T<sub>1/2</sub>. The rate of formation of tapentadol-O-glucuronide was also lower in subjects with increased hepatic impairment.</p> <p>Administered doses should be reduced in patients with moderate hepatic impairment (Child-Pugh Score 7 to 9), and its use is not recommended in severe hepatic impairment (Child-Pugh Score 10 to 15).</p>
Pregnancy / nursing	<p>Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Opioids cross the placenta and may produce respiratory depression in neonates; therefore, it is not for use in women during and immediately prior to labor.</p> <p>It is not known if tapentadol is excreted in breast milk. Physicochemical and available pharmacodynamic and toxicological data on tapentadol point to excretion in breast milk, and risk to the breastfeeding child cannot be excluded. A decision should be made whether to discontinue nursing or discontinue the drug.</p>
Children	The safety and efficacy in individuals less than 18 years of age have not been established.
Gender / Race	No gender- or race-specific differences in pharmacokinetic data have been identified.

## Dosage Forms

**Table 5. Availability, Storage and Handling<sup>1</sup>**



Dosage form	Strengths	Special handling or storage
Tablet	50 mg 100 mg 150 mg 200 mg 250 mg	Store up to 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).  Protect from moisture.  Keep in a secure place out of reach of children. Tablets that are no longer needed should be destroyed by flushing down the toilet.

**Dosage Range****Table 6. Dosing and Administration<sup>1</sup>**

Adult Dose	Pediatric Dose	Renal Dose	Hepatic Dose
<p><u>Pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate:</u></p> <p>Initial (opioid naïve or patients without opioid tolerance): 50 mg twice daily</p> <p>Initial (conversion from other opioids): no established conversion ratios defined by clinical trials</p> <p>Maintenance: titrate dose to efficacy in increments of 50 mg no more than twice daily every three days as necessary.</p> <p>Maximum: 250 mg twice daily</p> <p><u>Neuropathic pain associated with diabetic peripheral neuropathy in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate:</u></p> <p>Same dose recommendations</p>	<p>Safety and efficacy in pediatric patients less than 18 years of age have not been established.</p>	<p>No dose adjustment is recommended in mild or moderate renal impairment.</p> <p>Use is not recommended in patients with severe renal impairment.</p>	<p>No dose adjustment is recommended in mild hepatic impairment.</p> <p>Initiate treatment at 50 mg once daily with a maximum recommended dose of 100 mg per day in moderate hepatic impairment.</p> <p>Use is not recommended in patients with severe hepatic impairment.</p>

**Dosing Considerations<sup>1</sup>:**

- Discontinue all other tapentadol and tramadol products when initiating treatment and during treatment with Nucynta ER<sup>®</sup> (tapentadol extended-release).
- The maximum recommended dose of Nucynta ER<sup>®</sup> (tapentadol extended-release) is 500 mg per day, which is different from the maximum recommended dose of Nucynta<sup>®</sup> (tapentadol immediate-release) of 600 mg per day.

- Close monitoring is recommended when converting to Nucynta ER<sup>®</sup> (tapentadol extended-release) from methadone, as methadone has a long half-life and can accumulate in the plasma. The equianalgesic ratio between methadone and other opioids may vary widely as a function of previous dose exposure.
- Consideration should be given to initiating treatment in elderly patients toward the lower range of recommended doses, as they are more likely to have decreased renal and hepatic function.
- A ratio of 5:1 for Nucynta ER<sup>®</sup> (tapentadol extended-release):oxycodone ER has been used in clinical trials as relative equipotent dosing.<sup>6,7,10,12,13</sup>
- A ratio of 10:3 for Nucynta ER<sup>®</sup> (tapentadol extended-release):morphine ER has been used in a clinical trial as relative equipotent dosing.<sup>13</sup>
- A ratio of 10:0.03 for Nucynta ER<sup>®</sup> (tapentadol extended-release):fentanyl has been used in a clinical trial as relative equipotent dosing; however, this trial was conducted in Japan where a different formulation of fentanyl transdermal patch is available compared to the United States.<sup>13</sup>

## Precautions

### Boxed Warning for Nucynta ER<sup>®</sup> (tapentadol extended-release)<sup>1</sup>

WARNING	
<u>Addiction, Abuse, and Misuse</u>	Nucynta ER <sup>®</sup> (tapentadol extended-release) exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Nucynta ER <sup>®</sup> (tapentadol extended-release), and monitor all patients regularly for the development of these behaviors or conditions.
<u>Life-threatening Respiratory Depression</u>	Serious, life-threatening, or fatal respiratory depression may occur with use of Nucynta ER <sup>®</sup> (tapentadol extended-release). Monitor for respiratory depression, especially during initiation of Nucynta ER <sup>®</sup> (tapentadol extended-release) or following a dose increase. Instruct patients to swallow Nucynta ER <sup>®</sup> (tapentadol extended-release) tablets whole; crushing, chewing, or dissolving Nucynta ER <sup>®</sup> (tapentadol extended-release) can cause rapid release and absorption of a potentially fatal dose of tapentadol.
<u>Accidental Ingestion</u>	Accidental ingestion of even one dose of Nucynta ER <sup>®</sup> (tapentadol extended-release), especially by children, can result in a fatal overdose of tapentadol.
<u>Neonatal Opioid Withdrawal Syndrome</u>	Prolonged use of Nucynta ER <sup>®</sup> (tapentadol extended-release) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
<u>Interaction with Alcohol</u>	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Nucynta ER <sup>®</sup> (tapentadol extended-release). The co-ingestion of alcohol with Nucynta ER <sup>®</sup> (tapentadol extended-release) may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

**Table 8. Warnings/Precautions<sup>1</sup>**

<b>Warnings/Precautions</b>	Addiction, abuse and misuse; Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Nucynta ER <sup>®</sup> (tapentadol extended-release). Addiction can occur at recommended doses in addition to if the drug is purposefully misused or abused. Assess each patient's risk
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	<p>for opioid addiction, abuse or misuse prior to prescribing this agent, and monitor all patients receiving this agent for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse or mental illness. The potential for these risks should not, however, prevent the proper management of pain in any given patient. Abuse, or misuse of this agent by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of tapentadol and can result in overdose and death. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug.</p>
	<p>Life threatening respiratory depression; Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Life-threatening or fatal respiratory depression can occur at any time during the use of this medication. However, the risk is generally greatest during the initiation of therapy or following a dose increase. Individuals should be closely monitored for respiratory depression when initiating therapy and following dose increases.</p>
	<p>Neonatal opioid withdrawal syndrome; Prolonged use during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.</p>
	<p>Interactions with central nervous system (CNS) depressants; Hypotension, profound sedation, coma, respiratory depression, or death may result if Nucynta ER® (tapentadol extended-release) is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids, etc.). In addition, the patient's use of alcohol or illicit drugs that can cause CNS depression should be evaluated. If the decision to begin therapy with this agent, the starting dose should be 50 mg every 12 hours with frequent monitoring. Consideration should also be given to using a lower dose of the concomitant CNS depressant.</p>
	<p>Elderly, cachectic and debilitated patients; Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Patients should be monitored closely when initiating or titrating Nucynta ER® (tapentadol extended-release) as well as when this agent is given concomitantly with CNS depressants.</p>
	<p>Chronic pulmonary disease; Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression. Even at usual therapeutic doses, these agents may decrease respiratory drive to the point of apnea. Consideration should be given to the use of alternative non-opioid analgesics in these patients if possible.</p>
	<p>Hypotensive effects; Nucynta ER® (tapentadol extended-release) may cause severe hypotension. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Avoid use in patients with circulatory shock as it may cause</p>

	vasodilation that can further reduce cardiac output and blood pressure.
	Head injury or increased intracranial pressure; Monitor patients taking Nucynta ER® (tapentadol extended-release) who may be susceptible to the intracranial effects of carbon dioxide (CO <sub>2</sub> ) retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy. Nucynta ER® (tapentadol extended-release) may reduce respiratory drive, and the resultant CO <sub>2</sub> retention can further increase intracranial pressure. Avoid the use of this agent in patients with impaired consciousness or coma.
	Seizures; Nucynta ER® (tapentadol extended-release) has not been evaluated in patients with a predisposition to a seizure disorder. Tapentadol may exacerbate seizures in patients with seizure disorders, and may induce or aggravate seizures. Monitor patients with a history of seizure disorders for worsened seizure control during treatment with this agent.
	Serotonin syndrome; Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs. Serotonergic drugs comprise selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, drugs that affect the serotonergic neurotransmitter system (e.g. mirtazapine, trazodone, tramadol, etc.), and drugs that impair metabolism of serotonin including monoamine oxidase inhibitors (MAOIs). Serotonin syndrome may occur within the recommended dose and can be fatal.
	Gastrointestinal (GI) Conditions; Nucynta ER® (tapentadol extended-release) is contraindicated in patients with other GI obstruction, including paralytic ileus. Tapentadol may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.
	Avoidance of withdrawal; Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and buprenorphine) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, such as Nucynta ER® (tapentadol extended-release) as these agents can reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing therapy, gradually taper the dose. Do not abruptly discontinue medication.
	Driving and operating machinery; May impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Counsel patients not to drive or operate dangerous machinery unless they are tolerant to the effects and know how they will react to the medication.
	Hepatic impairment; A study with an immediate-release formulation of tapentadol in patients with hepatic impairment showed higher serum concentrations of tapentadol than in those with normal hepatic function. Avoid use of Nucynta ER® (tapentadol extended-release) in patients with severe hepatic impairment and reduce the dose in patients with moderate hepatic impairment, particularly when initiating and titrating the dose.
	Renal impairment; Use of Nucynta ER® (tapentadol extended-release) in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol.

**Contraindications**

Nucynta ER® (tapentadol extended-release) is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, known or suspected paralytic ileus, hypersensitivity (e.g., anaphylaxis, angioedema) to tapentadol or any other ingredients in the product, as well as among patients who are

receiving MAOIs or who have received them within the previous 14 days due to the additive effects of norepinephrine levels that may result in adverse cardiovascular (CV) events.

### Adverse Effects

Table 10 represents adverse reactions reported in  $\geq 2\%$  of subjects from both the open-label titration period and double-blind treatment period of a clinical trial for Nucynta ER® (tapentadol extended-release). Figures reported during the open-label titration phase are reported in the active drug column.

**Table 10. Adverse reactions reported by  $\geq 1\%$  of patients treated with tapentadol ER in three pooled, placebo-controlled trials of chronic low back pain and osteoarthritis**

Adverse Event	Nucynta ER® (tapentadol extended-release) 50 to 250 mg BID %; (N=980)	Placebo %; (N=993)
Nausea	12	7
Constipation	17	7
Dizziness	17	6
Headache	15	13
Somnolence	12	4
Fatigue	9	4
Vomiting	8	3
Dry mouth	7	2
Hyperhidrosis	5	<1
Pruritus	5	2
Insomnia	4	2
Dyspepsia	3	2
Lethargy	2	<1
Asthenia	2	<1
Anxiety	2	1
Appetite, decreased	2	<1
Vertigo	2	<1
Hot flush	2	<1
Disturbance in attention	1	<1
Tremor	1	<1
Chills	1	0
Abnormal dreams	1	<1
Depression	1	<1
Vision blurred	1	<1
Erectile dysfunction	1	<1

**Table 12. Adverse reactions reported by  $\geq 1\%$  of patients treated with tapentadol ER in two pooled, placebo-controlled trials of neuropathic pain associated with diabetic peripheral neuropathy**

Adverse Event	Nucynta ER (tapentadol) 50 to 250 mg BID %; (N=1,040)	Placebo %; (N=343)
Nausea	27	8
Dizziness	18	2
Somnolence	14	<1
Constipation	13	<1
Vomiting	12	3
Headache	10	5
Fatigue	9	<1
Pruritus	8	0

Adverse Event	Nucynta® ER (tapentadol) 50 to 250 mg BID %; (N=1,040)	Placebo %; (N=343)
Dry mouth	7	<1
Diarrhea	7	5
Appetite, decreased	6	<1
Anxiety	5	4
Insomnia	4	3
Hyperhidrosis	3	2
Hot flush	3	2
Tremor*	3	3
Abnormal dreams	2	0
Lethargy	2	0
Asthenia	2	<1
Irritability	2	1
Dyspepsia	1	0
Nervousness	1	0
Sedation	1	0
Vision blurred	1	0
Pruritis, generalized	1	0

### Drug Interactions

**Table 12. Drug Interactions<sup>1,18</sup>**

Interacting Medication or Disease	Interaction Severity Rating *	Potential Result
Naltrexone	Contraindicated	Concomitant use will result in precipitation of opioid withdrawal symptoms and decreased opioid effectiveness.
Monoamine oxidase inhibitors (MAOIs)	Contraindicated	May potentiate the effects of norepinephrine levels, which may result in adverse cardiovascular events. Concurrent use with MAOIs or use within 14 days of discontinuing MAOI treatment should be avoided.
Alcohol (ethanol)	Major	Concomitant use of alcohol may result in increased tapentadol plasma levels and potentially fatal overdose of tapentadol. Counsel patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol.
CNS Depressants (e.g., sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, alcohol, etc.)	Major	Concomitant use may increase the risk of respiratory depression, profound sedation, coma, and death. When used together, the dose of one or both agents should be reduced. Assess the duration of use of the CNS depressant and individual response, including the degree of tolerance that has developed to CNS depression. Start with Nucynta ER® (tapentadol extended-release) 50 mg every 12 hours, monitor closely, and consider using a lower dose of the concomitant CNS depressant.
Serotonergic agents (e.g., SSRIs, SNRIs, triptans, etc.)	Major	Concomitant use has resulted in serotonin syndrome according to post-marketing reports. If clinically warranted to use together, monitor closely, particularly with treatment initiation and dose adjustments.
Mixed Agonist/Antagonist	Major	Concomitant use may reduce the analgesic effect and/or precipitate withdrawal symptoms. Avoid concomitant



(pentazocine, nalbuphine, & butorphanol) and Partial Agonist (e.g., buprenorphine) Opioid Analgesics		administration.
Muscle Relaxants	Major	Tapentadol may result in enhanced neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Anticholinergics	Major	An increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus, may result from concurrent use with anticholinergic products.
Phenothiazines (e.g., chlorpromazine, promethazine, thioridazine, etc.)	Major	Concomitant use may result in increased CNS and respiratory depression.

\*Severity rating per Micromedex

### **Patient Monitoring Guidelines**<sup>1</sup>

Assess each patient's risk for opioid addiction, abuse, or misuse prior to initiating therapy and monitor all patients for the development of these behaviors or conditions. "Drug seeking" behaviors should also be monitored to help identify these potential concerns.

Continually re-evaluate patients to assess the maintenance of pain control and the development of adverse reactions. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics. Patients should be closely monitoring when transitioning to Nucynta ER® (tapentadol extended-release) from another opioid analgesic or from Nucynta ER® (tapentadol extended-release) to another opioid analgesic as there may be significant inter-patient variability in the relative potency of opioid therapies.

Continuously monitor patients for new or worsening adverse events or changes in medication efficacy, particularly with changes in drug doses and/or frequency. Closely monitor patients when there is the addition or elimination of other agents that may alter the efficacy or adverse event profile of the interacting agent(s). Individuals with renal and/or hepatic impairment as well as the elderly should have initial doses adjusted to account for impaired ability to metabolize and eliminate tapentadol and its metabolites. These individuals should be closely monitored as there is the increased risk of adverse events, particularly with changes in the underlying disease impairment and/or dose adjustments.

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