

Therapeutic Class Overview

Tramadol and Related Products

INTRODUCTION

- Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (International Association for the Study of Pain [IASP], 2012). Pain is a subjective experience that is unique to the individual and is difficult to identify or quantify by any observer. The type of pain being experienced is often classified by its pathophysiologic etiology. Somatic pain results from the activation of pain receptors in cutaneous or deep tissues (skin, bone, joint, or connective tissues) and is generally localized and described as sharp in nature. Visceral pain involves internal areas of the body (organs) and may be poorly localized and described as an aching pain. Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system (Baumann et al, 2014). An individual's reaction or response to treatment of pain can be highly variable. Pain thresholds are highly individualized among patients, and responses to therapy vary between patients and even within the same patient from day to day. Pain management is multifaceted and should incorporate both pharmacological and non-pharmacological measures.
- Tramadol (ULTRAM[®]) and tapentadol (NUCYNTA[®]) are both centrally-acting opioid analgesics that exert their analgesic effects through opioid agonist properties as well as by blocking the reuptake of norepinephrine and serotonin. Tramadol blocks norepinephrine and serotonin reuptake and has relatively weak μ -opioid receptor activity. Compared to tramadol, tapentadol has greater μ -opioid receptor activity, similar norepinephrine reuptake inhibitor activity, and weaker serotonin reuptake inhibitor activity (Tsutaoka et al, 2015).
- Tapentadol is a Schedule II controlled substance. In the past, tramadol was not classified as a controlled substance on the federal level; however, the Drug Enforcement Administration has moved tramadol-containing products into Schedule IV as of August 18, 2014 (Federal Register, 2014).
- Tapentadol may be associated with lower rates of gastrointestinal adverse events compared to other available opioid products. Tramadol is associated with reduced cardiovascular and respiratory side effects when compared to other opioids and appears to possess a low potential for abuse and psychological/physical dependence when used short term. However, cases of abuse and dependence have occurred, particularly in patients with a history of opioid abuse and those utilizing the tramadol-containing products long term (Leppert et al, 2005). Based on data reported to the National Poison Data System, tapentadol was associated with more toxic effects and severe outcomes than tramadol, consistent with an opioid agonist, whereas tramadol was associated with significantly higher rates of seizures and vomiting than tapentadol (Tsutaoka et al, 2015).
- This review includes all products that contain tramadol or tapentadol, including short-acting, long-acting, and combination products. Both tramadol and tapentadol are available in immediate-release and extended-release formulations. ULTRAM ER is an extended-release tablet formulation of tramadol, and CONZIP[™] is a capsule formulation that contains tramadol in a combination of immediate-release and extended-release components. In addition to immediate-release tablets, tapentadol is available as extended-release tablets. Tapentadol oral solution has been approved by the FDA, but has not been made available. Tramadol is also available in combination with acetaminophen as ULTRACET[®] and generics. Another tramadol formulation, RYZOLT[™], is a tablet formulation with both immediate-release and extended-release components. Please see Table 1 for information on product availability.
- One additional product in this class has been discontinued by its manufacturer and is not included within this review. RYBIX ODT[™] (tramadol orally disintegrating tablet) was FDA approved in May 2005 and was discontinued by the manufacturer in May 2013.
- Medispans class: Tramadol and tapentadol are classified within the opioid agonist class.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
NUCYNTA (tapentadol)	Depomed	Oral tablet: 11/20/2008 Oral solution: 10/15/2012*	-
NUCYNTA ER (tapentadol extended-release tablet)	Depomed	08/25/2011	-
ULTRAM (tramadol)	Various	03/03/1995	✓
ULTRAM ER† (tramadol extended-release tablet)	Various	09/08/2005	✓
RYZOLT† (tramadol extended-release tablet)	Various	12/30/2008	✓
CONZIP (tramadol extended-release capsule)	Vertical Pharmaceutical	05/07/2010	-‡
ULTRACET (tramadol/acetaminophen)	Various	08/15/2001	✓

* NUCYNTA oral solution has been approved by the FDA, but has not been launched.

† Brand-name RYZOLT and ULTRAM ER have been removed from the market, but generic versions remain available.

‡ Although no A-rated generics have been approved by the FDA, an authorized generic of CONZIP is marketed by Trigen Pharmaceuticals.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	NUCYNTA (tapentadol)	NUCYNTA ER (tapentadol ER)	ULTRAM (tramadol)	ULTRAM ER, CONZIP, RYZOLT (tramadol ER)	ULTRACET (tramadol/acetaminophen)
Management of moderate to moderately severe pain in adults for whom alternative treatments are inadequate			✓		
Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time and for whom alternative treatments are inadequate				✓	
Management of 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		✓			
Management of moderate to severe acute pain in adults for whom alternative treatments are inadequate	✓				
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate		✓			

Indication	NUCYNTA (tapentadol)	NUCYNTA ER (tapentadol ER)	ULTRAM (tramadol)	ULTRAM ER, CONZIP, RYZOLT (tramadol ER)	ULTRACET (tramadol/ acetaminophen)
Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate (indicated for short-term use of five days or less)					✓

(Prescribing information: CONZIP, 2016; NUCYNTA (oral solution), 2016; NUCYNTA (tablets), 2016; NUCYNTA ER, 2016; tramadol extended-release tablets, 2016; ULTRACET, 2016; ULTRAM, 2016; ULTRAM ER, 2016)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Tramadol

- Tramadol has been evaluated in various settings for the management of moderate-to-moderately severe pain:
 - In patients with symptomatic osteoarthritis (OA), tramadol (up to 400 mg daily) did not significantly improve the mean final pain intensity score compared to placebo when administered over three months (P=0.082); however, mean final pain relief score was superior in the tramadol group (0.43 vs -0.57; P=0.004), and both patient and investigator assessment of treatment favored tramadol over placebo (P=0.038 and P=0.001, respectively) (Fleischmann et al, 2001).
 - In patients with post-tonsillectomy pain, there was no statistically significant difference in visual analog scale (VAS) pain scores between tramadol and diclofenac over two weeks of treatment (P=0.66) (Courtney et al, 2001).
 - However, in some studies, tramadol has been demonstrated to be less effective than nonsteroidal anti-inflammatory drugs (NSAIDs). In studies by O'Donnell et al, a significantly greater proportion of patients with low back pain receiving celecoxib 200 mg twice daily achieved a ≥30% improvement from baseline in numeric rating scale (NRS)-pain scale scores compared to tramadol 50 mg administered four times daily (63.2 vs 49.9%; P<0.001 in one study and 64.1 vs 55.1%; P=0.008 in another study) (O'Donnell et al, 2009).
- Tramadol ER has been compared in clinical studies to placebo, immediate-release tramadol, and buprenorphine:
 - Tramadol ER formulations have consistently demonstrated significant improvements in pain scores compared to placebo in patients with moderate-to-moderately severe chronic pain (Burch et al, 2007; Kean et al, 2009; Fishman et al, 2007).
 - In one study, tramadol ER 300 mg significantly improved patient global assessment scores compared to placebo (P≤0.05); however, no improvements in Western Ontario and McMaster Universities (WOMAC) pain subscale scores were reported for tramadol ER 100 mg, 200 mg or 300 mg after 12 weeks of treatment (DeLemos et al, 2011).
 - Compared to tramadol, tramadol ER was associated with a significant reduction in VAS scores in an eight-week crossover study of patients with chronic pain (29.9 vs 36.2 mm; P<0.001) (Beaulieu et al, 2007).
 - In a 12-week study comparing tramadol ER to the buprenorphine transdermal patch, the least squares mean (LSM) change from baseline in Box Scale-11 pain score between treatments was -0.17 (95% CI, -0.89 to 0.54; P value not reported), which was within the non-inferiority margin, demonstrating that buprenorphine was non-inferior to tramadol ER in patients with OA of the hip or knee (Karlsson et al, 2009).
- The combination tramadol/acetaminophen (APAP) has been compared to placebo, other combination opioid/APAP products, and NSAIDs:
 - In patients with low back pain (N=318), the combination of tramadol/APAP was significantly more effective compared to placebo with regard to changes in VAS pain scores over three months (44.4 vs 52.3 mm; P=0.015) (Ruoff et al, 2003).

- In a study by Fricke et al comparing tramadol/APAP to hydrocodone/APAP in patients undergoing molar removal, both treatments provided statistically significant pain relief compared to placebo ($P < 0.024$); however, the differences were not significantly different from one another during the eight hour evaluation period (Fricke et al, 2002).
- In an eight-week study comparing tramadol/APAP to meloxicam or aceclofenac (not available in the U.S.) in patients with OA, there was a similar improvement in WOMAC pain scores between the treatment arms (6.75 vs 6.51, respectively; P value not reported). Similarly, there was no statistically significant difference in the percentage of patients who reported pain relief with tramadol/APAP compared to the NSAIDs (68.2 vs 78.7%; $P > 0.05$) (Park et al, 2012).
- Alfano et al reported that tramadol/APAP was associated with significantly lower visual rating scale pain scores compared to codeine/APAP (1.4 ± 0.76 vs 2.52 ± 0.86 ; $P < 0.001$) in patients undergoing surgical procedures; however, the trial was only two days in duration (Alfano et al, 2011).
- The results of a four-week trial in patients with low back pain demonstrated similar improvements in pain scores between tramadol/APAP and codeine/APAP (Mullican et al, 2001).

Tapentadol

- Several clinical studies have demonstrated the superior analgesic efficacy of tapentadol compared to placebo in the treatment of moderate to severe pain (Daniels et al, 2009; Hale et al, 2009; Hartrick et al, 2009; Kleinert et al, 2008; Lee et al, 2014; Stegman et al, 2008). In addition to reducing pain intensity and providing pain relief, therapy with tapentadol was associated with a shorter time to 50% pain relief, a longer time to first dose of rescue medication, a decrease in the use of rescue medications, and a greater number of treatment responders compared to placebo (Daniels et al, 2009; Kleinert et al, 2008; Lee et al, 2014; Stegman et al, 2008).
- Several trials compared the efficacy of tapentadol to oxycodone:
 - In one study of patients who were candidates for joint replacement surgery, tapentadol significantly reduced pain intensity scores compared to placebo and was noninferior to oxycodone for analgesia. In addition, the incidence of gastrointestinal-related adverse events was significantly lower with tapentadol compared to oxycodone ($P < 0.001$) (Hartrick et al, 2009).
 - In a short-term (four day) study of postoperative pain in patients who had undergone bunionectomy, both tapentadol and oxycodone significantly lowered summed pain intensity scores after three days of treatment compared to placebo ($P \leq 0.05$ for all); however, only the tapentadol 100 mg doses demonstrated statistically significant differences compared to placebo on day four ($P = 0.0284$). Tapentadol treatment was associated with a reduction in nausea, dizziness, vomiting, and constipation compared to oxycodone (P values not reported) (Stegman et al, 2008).
 - A three-month safety study by Hale et al demonstrated a lower incidence of treatment-related adverse events with tapentadol compared to oxycodone, while also significantly lowering the incidence of withdrawal symptoms (17 vs 29%; $P \leq 0.05$) (Hale et al, 2009).
 - A short-term (ten day) study in patients with low back pain and associated radicular leg pain demonstrated that pain relief with tapentadol was non-inferior to that of oxycodone. In this study, tapentadol was associated with a lower incidence of vomiting and constipation (Biondi et al, 2013).
- The effectiveness of the extended-release formulation of tapentadol has been demonstrated in several clinical trials:
 - In a 12-week trial of adults with OA of the knee, significant pain relief was achieved with tapentadol ER compared to placebo (LSM difference, -0.7; 95% CI, -1.04 to -0.33). Oxycodone controlled-release (CR) reduced the average pain intensity compared to placebo for the overall maintenance period (LSM difference vs placebo, -0.3), but was not statistically significantly lower at week 12 of the maintenance period (LSM, -0.3; P value not reported). There was no significant difference in the proportion of patients in the tapentadol group and the placebo group achieving a $\geq 30\%$ reduction in average pain intensity at week 12 of the maintenance period (43 vs 35.9%, respectively; $P = 0.058$). Significantly fewer patients in the oxycodone CR group achieved this improvement compared to placebo (24.9 vs 35.9%; $P = 0.002$). A higher percentage of patients achieved a $\geq 50\%$ reduction in average pain intensity from baseline at week 12 with tapentadol ER compared to placebo (32 vs 24.3%; $P = 0.027$), while significantly fewer oxycodone CR-treated patients achieved this improvement compared to placebo (17.3 vs 24.3%; $P = 0.023$) (Afilalo et al, 2010).
 - Buynak et al evaluated tapentadol ER compared to oxycodone ER and placebo in adults with moderate to severe lower back pain. The mean change in pain intensity from baseline to week 12 was significantly greater for tapentadol ER (LSM difference, -0.8; $P < 0.001$) and oxycodone CR (LSM difference, -0.9; $P < 0.001$) compared to placebo. The mean change in pain intensity from baseline over the entire maintenance period

- was -2.8 for the tapentadol ER group and -2.1 for the placebo group (LSM difference, -0.7; $P < 0.001$) (Buynak et al, 2010).
- Schwartz et al evaluated tapentadol ER in adults with painful diabetic peripheral neuropathy in a 12-week, randomized withdrawal trial. Patients were titrated to an optimal dose of tapentadol ER during a three-week open-label phase; subsequently, patients with at least a one-point reduction in pain intensity were randomized to continue tapentadol ER or switch to placebo during a 12-week double-blind phase. The LSM change in average pain intensity from the start of the double-blind treatment period to week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0 in the tapentadol ER group, indicating no change in pain intensity (LSM difference, -1.3; 95% CI, -1.7 to -0.92; $P < 0.001$). From pre-titration to week 12 of double-blind treatment, a $\geq 30\%$ improvement in pain intensity was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients ($P = 0.017$). A $\geq 50\%$ improvement in pain intensity was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients ($P = 0.028$) (Schwartz et al, 2011).
 - A second, 12-week, randomized withdrawal trial of tapentadol ER in adults with painful diabetic peripheral neuropathy was performed by Vinik et al. In this trial, the mean change in average pain intensity from the start of the double-blind treatment period to week 12 was 1.3 in the placebo group, indicating a worsening in pain intensity, and 0.28 in the tapentadol ER group (LSM difference, -0.95; 95% CI, -1.42 to -0.49; $P < 0.001$). From pre-titration to week 12 of double-blind treatment, a $\geq 30\%$ improvement in pain intensity was observed in 55.4% of tapentadol ER-treated patients and 45.4% of placebo-treated patients ($P = 0.032$). A $\geq 50\%$ improvement in pain intensity was observed in 40.4% of tapentadol ER-treated patients and 28.9% of placebo-treated patients ($P = 0.015$) (Vinik et al, 2014).
 - Kress et al evaluated tapentadol ER compared to placebo and morphine CR for managing moderate to severe malignant tumor-related pain. Patients were randomized and titrated to an optimal dose of tapentadol ER (100 mg to 250 mg twice daily) or morphine sulfate CR (40 mg to 100 mg twice daily) over two weeks. Patients who completed titration and had adequate pain control continued into a four-week maintenance period during which patients who received morphine CR continued on the same medication and patients who received tapentadol ER were re-randomized to continue tapentadol ER or switch to placebo. Criteria for response during each phase were based on completion of the phase, a pain intensity score < 5 , and a mean total daily dose of ≤ 20 mg/day of rescue medication (morphine sulfate immediate release). Based on responder rates at the end of titration, tapentadol ER was determined to be non-inferior to morphine sulfate CR (76% vs 83%, respectively). During the titration phase, incidences of treatment-related adverse events were 50% with tapentadol ER and 63.9% with morphine CR; nausea, vomiting, and dry mouth occurred less commonly with tapentadol ER than with morphine CR. During the maintenance phase, the adjusted responder rate was significantly higher with tapentadol ER (64.3%) than with placebo (47.1%) ($P = 0.02$). (Kress et al, 2014).
 - Imanaka et al evaluated tapentadol ER compared to oxycodone CR in Japanese and Korean patients with cancer-related pain. The primary efficacy endpoint, mean change in average pain intensity on an 11-point scale, was -2.69 and -2.57 in the tapentadol ER and oxycodone CR groups, respectively. Tapentadol was demonstrated to be non-inferior to oxycodone CR for the primary endpoint. The percentage of patients responding with $\geq 30\%$ reduction in pain intensity was 63.5% and 59% in the tapentadol ER and oxycodone CR groups, respectively, and the percentage responding with a $\geq 50\%$ improvement was 50% and 42.4%, respectively. In this study, tapentadol was also associated with a slightly lower incidence of some gastrointestinal adverse events than oxycodone CR (Imanaka et al, 2013).
 - In a pooled analysis of three studies of patients with pain due to OA or nonmalignant lower back pain, tapentadol ER was significantly more effective compared to placebo over a three week treatment phase (LSM difference, -0.6; 95% CI, -0.8 to -0.39; $P < 0.001$) and for the overall 12 week maintenance period (-0.5; 95% CI, -0.73 to -0.34; $P < 0.001$). A similar analgesic effect was reported in patients receiving oxycodone CR; however, the responder rate was higher with tapentadol ER ($P < 0.001$). Moreover, a significantly higher proportion of patients receiving tapentadol ER achieved a $\geq 30\%$ and $\geq 50\%$ improvement in pain intensity from baseline compared to oxycodone CR and placebo ($P < 0.001$ for both) (Lange et al, 2010).
 - No published studies were identified that compared the analgesic efficacy of tramadol and tapentadol.

Guidelines

- Current consensus guidelines for the management of low back pain recommend the use of opioids or tramadol in patients with severe pain that has not responded to treatment with acetaminophen or NSAIDs (Chou et al, 2007).
- Tramadol may be an initial treatment option along with topical capsaicin and topical or oral NSAIDs for osteoarthritis of the hand, knee or hips (Hochberg et al, 2012).
- Guidelines established by the European Federation of Neurological Societies and the American Academy of Neurology generally recommend the use of tramadol as a second-line therapy for the treatment of various polyneuropathies (Attal et al, 2010; Bril et al, 2011).
- A practice guideline from the American College of Occupational and Environmental Medicine (ACOEM) notes that tramadol may be a better option than more potent opioids for management of chronic noncancer pain. However, it notes that with long-term use, especially at higher doses, it may be considered equivalent to other opioids (Hegmann et al, 2014).
- Based on an updated systematic review and meta-analysis, the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain gives tramadol a weak recommendation for use in the management of neuropathic pain, recommending it as a second-line agent. Medications with a strong recommendation for use (first-line agents) include gabapentin, pregabalin, duloxetine, venlafaxine, and tricyclic antidepressants. Tapentadol has an inconclusive recommendation for neuropathic pain based on inconsistent findings (Finnerup et al, 2015).
- The Canadian Pain Society also recommends tramadol as a second-line agent for management of chronic neuropathic pain, and recommends tapentadol as a fourth-line agent. First-line agents include gabapentin, pregabalin, serotonin noradrenaline reuptake inhibitors, and tricyclic antidepressants (Moulin et al, 2014).
- The specific role of immediate- or extended-release tapentadol has not been incorporated into most currently available treatment guidelines, and in most cases no preference is given to one single opioid over another.

SAFETY SUMMARY

- NUCYNTA ER is included in the Extended Release/Long Acting (ER/LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS). The REMS consists of a medication guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. The goal of the REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications (FDA, 2016).
- Tapentadol is a Schedule II controlled substance, and **tapentadol-containing products** carry a Boxed Warning regarding the risks of addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion; **interaction with benzodiazepines and other central nervous system (CNS) depressants**; and neonatal opioid withdrawal syndrome (NOWS). Tramadol is a Schedule IV controlled substance, and **ULTRAM, ULTRAM ER, and ULTRACET** carry Boxed Warnings regarding these same risks, with the addition of concomitant use of cytochrome P450 (CYP) inducers and inhibitors.
- ULTRACET has a Boxed Warning noting that acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death.
- **Tapentadol- and tramadol-containing products are generally contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma where resuscitation is unfeasible, known or suspected gastrointestinal obstruction, hypersensitivity, and with concurrent use of monoamine oxidase inhibitors (MAOIs) within the last 14 days.**
- The prescribing information for both tramadol and tapentadol contain warnings regarding the risk of seizures and serotonin syndrome in patients using concomitant serotonergic drugs. **Based on data reported to the National Poison Data System, tramadol is associated with a greater risk of seizures than tapentadol (Tsutaoka et al, 2015).**
- Both tramadol and tapentadol have warnings related to respiratory depression and CNS depression, and may have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause CNS depression. However, tramadol appears to be associated with reduced cardiovascular and respiratory side effects when compared to opioids and appears to possess a low potential for abuse and psychological/physical dependence when used short term. However, cases of abuse and dependence have occurred, particularly in patients with a history of opioid abuse and those utilizing the tramadol containing products long term (Leppert et al, 2005). **Based on data reported to the National Poison Data System,**

tapentadol was associated with more toxic effects and severe outcomes than tramadol, consistent with an opioid agonist (Tsutaoka et al, 2015).

- Tramadol- and tapentadol-containing products may produce adrenal insufficiency, severe hypotension, and increased intracranial pressure.
- Tapentadol may be associated with lower rates of gastrointestinal adverse events compared to other available opioid products. Tramadol is associated with a higher risk of vomiting than tapentadol (Tsutaoka et al, 2015).
- Notable drug interactions associated with tramadol and/or tapentadol include:
 - Concomitant use with MAOIs may lead to an increased risk of seizures or serotonin syndrome; use only with great caution.
 - Additive serotonergic effects may occur when co-administered with serotonergic drugs.
 - CYP3A4 and/or CYP2D6 inhibitors may reduce the metabolism of tramadol, thereby increasing the risk of adverse events. Carbamazepine increases tramadol metabolism and may significantly reduce its analgesic efficacy.
 - Tapentadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
NUCYNTA NUCYNTA ER (tapentadol)	<p>Immediate release (IR) tablet: 50 mg 75 mg 100 mg</p> <p>Extended-release (ER) tablet: 50 mg 100 mg 150 mg 200 mg 250 mg</p> <p>Oral solution: 20 mg/mL (not marketed)</p>	<p><u>Acute Pain:</u> IR tablet and oral solution: initial, 50 mg, 75 mg, or 100 mg every four to six hours</p> <p><u>Chronic pain, Neuropathic pain:</u> ER tablet: initial, 50 mg twice daily; maintenance, titrate to adequate analgesia</p>	<p><u>Max dose:</u> IR tablet and oral solution: 700 mg on first day, 600 mg on subsequent days ER tablet: 500 mg/day</p> <p>IR tablet and oral solution: On first day of dosing, second dose may be administered as soon as 1 hour after the first dose if adequate pain relief is not attained with the first dose</p>	<p>May be given with or without food</p> <p><u>ER tablets:</u> Advise patients to swallow whole and not to cut, chew, dissolve, or crush the tablet</p>
ULTRAM ULTRAM ER CONZIP RYZOLT (tramadol)	<p>Tablet: 50 mg</p> <p>ER tablet: 100 mg 200 mg 300 mg</p> <p>ER capsule: 100 mg 150 mg 200 mg 300 mg</p>	<p><u>Management of moderate to moderately severe pain in adults:</u> IR tablet: initial, 25 to 50 mg in the morning titrated to four times daily; maintenance, 50 to 100 mg every four to six hours as needed</p> <p><u>Chronic pain:</u> ER capsule, ER tablet (patients not currently on tramadol IR)</p>	<p><u>Max dose:</u> IR: 400 mg/day ER: 300 mg/day</p>	<p>Administer without regard to meals</p> <p><u>ER capsules and ER tablets:</u> Advise patients to swallow whole and not to cut, chew, dissolve, or crush the capsule or tablet.</p>

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		products): initial, 100 mg daily and titrated to pain relief ER capsule, ER tablet (patients currently on tramadol IR products): initial, calculate the 24-hour tramadol IR dose and round down to nearest 100 mg increment and administer daily		
ULTRACET (tramadol/acetaminophen)	Tablet: 37.5 mg/325 mg	<u>Short-term (five days or less) management of acute pain:</u> Tablet: initial, two tablets every four to six hours as needed for five days or less	<u>Max dose:</u> Eight tablets daily	Take without regard to food; take with food if GI upset occurs

ER=extended release, IR=immediate release

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
NUCYNTA NUCYNTA ER (tapentadol)	Consider starting elderly patients with the lower range of recommended doses	Safety and efficacy have not been established in pediatric patients younger than 18 years; use is not recommended in this population	Mild to moderate: No dosage adjustment is recommended Severe: Use is not recommended	Mild: No dosage adjustment is recommended Moderate: IR: 50 mg with the interval between doses no less than every 8 hours. Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval, max 3 doses in 24 hours (150 mg per 24 hours). ER: 50 mg	Pregnancy Category C Unknown whether excreted in breast milk; use is not recommended

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
				administered no more frequently than once every 24 hours, max 100 mg/day Severe: Use is not recommended	
ULTRAM ULTRAM ER CONZIP RYZOLT (tramadol)	<u>Elderly >65 years:</u> Use caution and initiate at the lower end of the dosing range; refer to adult dosing <u>Elderly >75 years:</u> IR: Do not exceed 300 mg/day; see dosing adjustments for renal and hepatic impairment ER: Use with great caution; see dosing for adults, renal, and hepatic impairment	Safety and efficacy have not been established	IR: CrCl <30 mL/minute: Administer 50 to 100 mg every 12 hours (max 200 mg/day) ER: Should not be used in patients with CrCl <30 mL/minute	IR: Recommended dose in patients with cirrhosis: 50 mg every 12 hours ER: Should not be used in patients with severe (Child-Pugh class C) hepatic dysfunction (ULTRAM ER, CONZIP) or any degree of hepatic dysfunction (RYZOLT [generic])	Pregnancy Category C (RYZOLT) Unclassified† (ULTRAM, ULTRAM ER, and CONZIP) Prolonged use of opioids during pregnancy may cause NOWS. Available data in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. Excreted in breast milk; use is not recommended
ULTRACET (tramadol/ acetaminophen)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients	Safety and efficacy in pediatric patients ≤16 years of age have not been established	CrCl<30 mL/minute: Maximum of two tablets every 12 hours.	Not recommended	Unclassified† Available data in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. Excreted in breast milk; use is not recommended.

CrCl=creatinine clearance, ER=extended release, IR=immediate release

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Tramadol (ULTRAM) and tapentadol (NUCYNTA) are both centrally-acting opioid analgesics that produce analgesia through opioid agonist properties and by blocking the reuptake of norepinephrine and serotonin.
- Both tramadol and tapentadol are available in extended-release formulations, and tramadol is also available in combination with acetaminophen. Tramadol is available generically in immediate-release (IR) and extended-release formulations as well as in combination with acetaminophen. Currently, there is no generic available for tapentadol-containing products.
- Clinical studies have generally demonstrated that tramadol and tapentadol are effective in the management of moderate-to-moderately severe chronic pain and for the relief of moderate-to-severe conditions of acute pain including low back pain, osteoarthritis, and diabetic peripheral neuropathy. Clinical studies evaluating tapentadol (both IR and ER) have generally demonstrated significant pain relief compared to placebo with a similar analgesic profile compared to oxycodone (both IR and ER). Furthermore, both formulations of tapentadol may be associated with a more favorable adverse event profile compared to oxycodone. There is a risk of seizures with both tramadol and tapentadol products; however, the risk appears to be higher with tramadol. Tapentadol products are classified as Schedule II controlled substances, and tramadol-containing products are classified as schedule IV controlled substances.
- Guidelines for the treatment of low back pain recommend opioids or tramadol in patients with severe pain that has not responded to treatment with acetaminophen or NSAIDs (Chou et al, 2007). Tramadol may be considered an initial treatment option along with topical capsaicin and topical or oral NSAIDs for osteoarthritis of the hand, knee or hips (Hochberg et al, 2012). Guidelines established by the European Federation of Neurological Societies and the American Academy of Neurology generally recommend tramadol as a second-line therapy for the treatment of polyneuropathies (Attal et al, 2010, Bril et al, 2011). Guidelines from the International Association for the Study of Pain and the Canadian Pain Society recommend tramadol as a second-line agent for neuropathic pain (Finnerup et al, 2015; Moulin et al, 2014). A practice guideline from the American College of Occupational and Environmental Medicine states that tramadol may be a better option than more potent opioids for management of chronic noncancer pain, but may be an equivalent choice when used long-term (Hegmann et al, 2014). The role of immediate- or extended-release tapentadol is not specifically incorporated into most currently available treatment guidelines, and in most cases no preference is given to one single opioid over another.

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