

Tapentadol IR: A Gain for Pain?

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BIOLOGICALS

Learning Objectives

1. Describe the mechanism of action of tapentadol immediate release (IR).
2. Determine the appropriate dose and dosing schedule for tapentadol IR.
3. Recognize tapentadol IR's contraindications, warnings and precautions.
4. Identify adverse effects that have been associated with tapentadol IR.
5. Discuss potential drug-drug interactions with tapentadol IR.

Introduction

Pain is the most common reason that patients seek medical care.¹ Pain may be acute or chronic.^{1,2} Acute pain is generally associated with an identifiable cause, resolves after the removal of the cause, responds to treatment, and lasts less than 1 to 3 months.^{1,3} Pain that does not have a clear cause or that lasts longer than 1 to 3 months is considered chronic pain.^{1,3} Pharmacological treatment for pain includes nonopioid analgesics, such as salicylates, acetaminophen and non-steroidal anti-inflammatory drugs, opioids, and other drug classes, including antidepressants and anticonvulsants.²

Tapentadol immediate release (IR) (Nucynta[®]; Johnson & Johnson Pharmaceutical Research and Development, marketed by the PriCara division of Ortho-McNeil-Janssen), was approved on November 20, 2008, by the United States Food and Drug Administration (FDA) for the treatment of moderate to severe acute pain in adults.⁴⁻⁶ Tapentadol IR is the first oral centrally acting analgesic to be approved in the United States in more than a decade.^{7,8} Tapentadol has been placed into schedule II of the Controlled Substances Act.⁴ At the time of this writing, tapentadol IR was not on the market. An extended-release formulation is currently in late-stage clinical development.⁹

Mechanism of Action and Pharmacokinetics

Tapentadol IR is a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor, both of which are believed to contribute to the drug's analgesic efficacy, although the exact mechanism is unknown.¹⁰ The only other mu-opioid receptor agonist/reuptake inhibitor available in the United States is tramadol, which inhibits the reuptake of serotonin in addition to norepinephrine.^{2,11} The structure of tapentadol IR is unlike that of opioids such as morphine and is most similar to tramadol (Figure 1¹¹⁻¹³).^{14,15} The pharmacokinetics of tapentadol IR are shown in Table 1.¹⁰

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Table 1. Pharmacokinetics of tapentadol IR.¹⁰

Mean absolute bioavailability after single-dose administration (fasting)	32%
Time to maximum serum concentration	1.25 hours
Volume of distribution (of intravenous dose)	540 ± 98 L
Plasma protein binding (of intravenous dose)	20%
Metabolism	Primarily phase 2 glucuronidation
Excretion	Primarily renal (99%)
Terminal half-life	4 hours
Total clearance	1530 ± 177 ml/min

Clinical Trials

Johnson & Johnson submitted data from twenty phase 1, six phase 2 and seven phase 3 trials to the FDA to support tapentadol IR's approval.¹⁶ Two phase-2 trials^{17,18} and four phase-3 trials¹⁹⁻²² were published at the time of this writing. The studies by Daniels and colleagues¹⁹ and Hartrick and colleagues²¹ were considered pivotal studies for the approval of tapentadol IR.²³ Five of the published trials are primarily efficacy studies and are summarized in Table 2; the sixth trial²² is primarily a tolerability study in which efficacy was evaluated as a secondary endpoint. All of the published studies are short-term, randomized, double-blind, placebo-controlled studies except for the tolerability trial,²² which lasted 90 days and did not have a placebo group.

Published efficacy studies of tapentadol IR (see Table 2) showed significant improvement in pain compared to placebo. Higher doses of tapentadol IR appeared to have similar efficacy to the doses of morphine and oxycodone evaluated during the trials. However, statistical analyses were only performed on each of these agents versus placebo; the statistical significance of tapentadol IR's efficacy versus that of morphine and oxycodone was not determined.

Adverse Effects

The adverse effect (AE) profile of tapentadol IR is similar to that of other mu-opioid agonists. The most serious AE of opioids is respiratory depression; other common AEs are sedation, dizziness, nausea, vomiting, itching, sweating and constipation.²

The results of a phase 3 tolerability study by Hale and colleagues²² suggest that tapentadol IR may have a more favorable gastrointestinal (GI) tolerability profile than 10-15 mg oxycodone immediate release (IR). In this 90-day, randomized, double-blind study, 878 patients with lower back pain or osteoarthritis of the hip or knee were randomized to tapentadol IR 50 mg or 100 mg (n = 703) or oxycodone IR 10-15 mg (n = 175) every 4 to 6

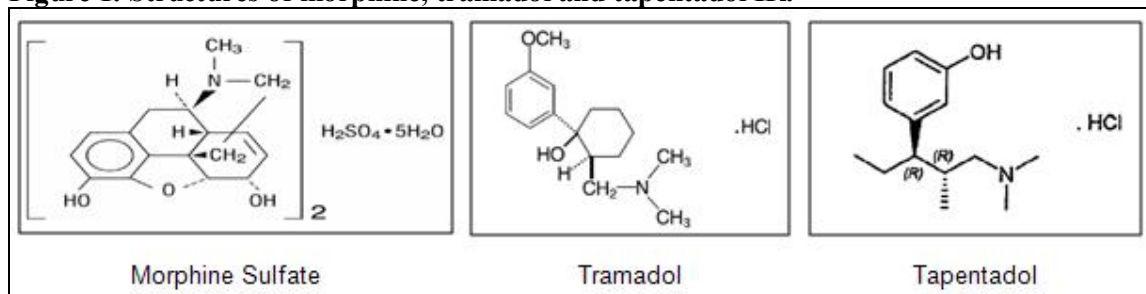
hours as needed. A higher percentage of patients in the tapentadol IR group (57.6% versus 50.6% in the oxycodone group) completed the study. The mean total daily doses were 284 mg in the tapentadol IR group and 42 mg in the oxycodone group.

Overall, 76.3% of patients in the tapentadol IR

group experienced treatment-emergent AEs compared to 82.9% in the oxycodone group. Adverse effects occurring in × 5% of patients in either group were GI disorders (nausea, vomiting, diarrhea and constipation), dizziness, headache, somnolence, fatigue, dry mouth and pruritus. Odds ratios [95% confidence interval] showed that patients treated with tapentadol IR were significantly less likely (nominal p < 0.001) to experience nausea (OR 0.542 [0.37-0.79]), vomiting (OR 0.476 [0.32-0.70]) and constipation (OR 0.396 [0.26-0.59]). The percentage of patients who discontinued due to AEs was lower in the tapentadol IR group (20.8%) than in the oxycodone group (30.6%). AEs that caused discontinuation in at least 2% of patients were nausea, vomiting, constipation, somnolence, headache and pruritus. GI disorders (nausea, vomiting, and constipation) caused fewer discontinuations in the tapentadol IR group (8.8%) than in the oxycodone group (21.2%).

Patients in published efficacy studies¹⁷⁻²¹ experienced AEs similar to those in the tolerability study. Nausea, vomiting and constipation generally occurred less frequently in patients who received tapentadol IR than in patients who received morphine or oxycodone. In pooled safety data from nine phase 2 and 3 studies, the most common AEs (observed in × 5% of patients who received tapentadol IR) were nausea (30%), dizziness (24%), vomiting (18%), somnolence (15%), constipation (8%) and pruritus (5%).¹⁰

Use of tapentadol IR may lead to dependence, and withdrawal symptoms may occur if the drug is discontinued abruptly.¹⁰ This is more likely to occur the longer the patient receives the drug. In the tapentadol IR tolerability study,²² the large majority of patients (82.7%) who discontinued tapentadol IR after taking it up to 90 days did not experience

Figure 1. Structures of morphine, tramadol and tapentadol IR.¹¹⁻¹³

opioid withdrawal.¹⁰ Moderate withdrawal symptoms were experienced by 0.3% of the patients in this study, while 17% experienced mild withdrawal symptoms.¹⁰

Drug Interactions

Tapentadol IR is contraindicated in patients who are taking monoamine oxidase inhibitors (MAOIs) or who have taken them within the last 14 days.¹⁰ The potential additive effects could increase norepinephrine levels, which could lead to adverse cardiovascular events or serotonin syndrome.¹⁰ Similarly, the drug should be used with caution with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SRNIs), tricyclic antidepressants (TCAs), triptans and other drugs that impair serotonin metabolism due to the risk of serotonin syndrome.¹⁰ Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular aberrations and/or GI symptoms.¹⁰

Additive effects may also occur when tapentadol IR is concurrently given with other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics or other central nervous system (CNS) depressants (including alcohol).¹⁰ If these drugs are taken in combination with tapentadol IR, additive effects may result in respiratory depression, hypotension, profound sedation, coma or death. When therapy with tapentadol IR and one of these agents is necessary, a reduction in the dose of one or both agents should be considered.¹⁰

There are no known clinically significant pharmacokinetic drug interactions with tapentadol IR.¹⁰ Tapentadol IR does not appear to inhibit or induce the cytochrome P450 enzymes, it is not significantly metabolized via the P450 system and it is not highly protein bound; for these reasons the likelihood of pharmacokinetic drug-drug interactions is thought to be low.¹⁰

Contraindications, Warnings and Precautions

Tapentadol IR is contraindicated in patients with significant respiratory depression and in patients with acute or severe bronchial asthma or hypercapnia if such patients are in unmonitored settings when resuscitative equipment is unavailable; in patients with paralytic ileus; and in patients who are receiving MAOIs or who have taken them within the last 14 days.¹⁰

Tapentadol IR should be used with caution in patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve; in patients receiving other drugs that can cause CNS depression; in patients with head injury and increased intracranial pressure; in patients with a history of seizure disorder or who have a condition that puts them at risk of seizures; and in patients who have biliary tract disease, including acute pancreatitis.¹⁰

Tapentadol IR is a mu-opioid receptor agonist, and, as such, has the potential to be abused and cause overdose or

death. Patients receiving tapentadol IR should be monitored for signs of abuse and addiction.¹⁰

Patients receiving tapentadol IR should be cautioned that the drug may impair their ability to drive or operate machinery, especially at the beginning of treatment or if combined with alcohol or other CNS depressants, including illicit drugs.¹⁰

Tapentadol IR is in pregnancy category C.¹⁰ There are no well controlled studies in pregnant women. Tapentadol IR should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. The drug is not recommended immediately before or during labor and delivery.¹⁰ Newborns whose mothers have been taking tapentadol IR should be monitored for respiratory depression, and an opioid antagonist should be available. Tapentadol IR should not be used during breast feeding.¹⁰ Limited information is available on the excretion of tapentadol IR into human or animal milk. Available data suggest that tapentadol IR is excreted into breast milk, and a risk to a nursing infant cannot be excluded.¹⁰

Availability and Dosing

Tapentadol IR will be available in 50, 75 and 100 mg immediate-release tablets for oral administration.¹⁰ The drug must be dispensed with a Medication Guide.¹⁶ The recommended dose is 50 mg, 75 mg or 100 mg every 4 to 6 hours depending on pain intensity.¹⁰ The drug may be taken with or without food. On the first day of dosing, if adequate pain relief is not achieved with the first dose, the second dose may be administered as soon as one hour after the first dose. Subsequent dosing is 50 mg, 75 mg or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability.¹⁰ The maximum recommended daily dose is 700 mg on the first day and 600 mg on subsequent days. The labeling for tapentadol IR states that withdrawal symptoms may be reduced if tapentadol IR is tapered before it is discontinued;¹⁰ however, no specific tapering schedule is provided.

No dosage adjustment is recommended in patients with mild or moderate renal impairment or in patients with mild hepatic impairment. Tapentadol IR should be used with caution in patients with moderate hepatic impairment.¹⁰ In these patients, tapentadol IR should be initiated at 50 mg no less than every 8 hours (maximum of 3 doses in 24 hours). Subsequent dosing should be adjusted to maintain analgesia with acceptable tolerability and can be achieved by either shortening or lengthening the dosing interval.

Generally no dosage adjustment is recommended for elderly patients with normal renal and hepatic function; however, because elderly patients are more likely to have decreased renal and hepatic function, starting elderly patients at the lower range of the recommended doses should be considered.¹⁰

When used in combination with other CNS depressants, consideration should be given to reducing the dose of one or

both drugs. Tapentadol IR has not been studied in patients younger than 18 years, or in patients with severe renal and hepatic impairment; therefore use in these populations is not recommended.¹⁰

Table 2. Tapentadol IR efficacy trials.^{17-19,21}

Author, Year N Phase	Pain State Primary Endpoint Length Frequency of Administration	Treatment Groups (N)	Primary Endpoint Results
Kleinert, 2008 ¹⁷ n = 400 Phase 2	Post-surgical dental (third mandibular tooth extraction) TOTPAR over 8 hours Single dose	TAP IR 25 mg (n = 49) TAP IR 50 mg (n = 50) TAP IR 75 mg (n = 50) TAP IR 100 mg (n = 48) TAP IR 200 mg (n = 50) MS 60 mg (n = 51) IBU 400 mg (n = 51) PBO (n = 51)	NS 7.9 [8.1] (p = 0.041) 9.7 [8.5] (p = 0.001) 11.6 [8.5] (p < 0.001) 15.3 [8.2] (p < 0.001) 13.8 [10.3] (p < 0.001) 17.9 [9.9] (p < 0.001) 4.7 [7.3] Results reported as mean [SD] score (p-value versus placebo)
Stegmann, 2008 ¹⁸ n = 269 Phase 2	Post-surgical (bunionectomy) SPI over 24 hours 72 hours Every 4 to 6 hours	TAP IR 50 mg (n = 67) TAP IR 100 mg (n = 68) OXY IR 10 mg (n = 67) PBO (n = 67)	33.6 [17.9] (p = 0.0133) 29.2 [15.2] (p = 0.001) 25.7 [17.2] (nominal p = 0.0365) 41.9 [17.7] Results reported as mean [SD] score (p-value versus placebo)
Daniels, 2009 ¹⁹ n = 603 Phase 3	Post-surgical (bunionectomy) SPID over 48 hours 72 hours Every 4 to 6 hours	TAP IR 50 mg (n = 119) TAP IR 75 mg (n = 120) TAP IR 100 mg (n = 118) OXY IR 15 mg (n = 125) PBO (n = 121)	119.1 [125.86] (p < 0.001) 139.1 [118.93] (p < 0.001) 167.2 [98.99] (p < 0.001) 172.3 [110.86] (p < 0.001) 24.5 [120.93] Results reported as mean [SD] score (p-value versus placebo)
Daniels, 2009 ²⁰ n = 901 Phase 3	Post-surgical (bunionectomy) SPID over 48 hours 72 hours Every 4 to 6 hours	TAP IR 50 mg (n = 275) TAP IR 75 mg (n = 278) OXY IR 10 mg (n = 279) PBO (n = 69)	62.4 (95% CI, 39.01-125.70) 84.6 (95% CI, 61.29-107.96) 81.5 (95% CI, 58.13-104.79) — Results reported as least squares mean difference from placebo; all p < 0.001
Hartrick, 2009 ²¹ n = 674 Phase 3	End-stage DJD (hip or knee) -awaiting joint replacement SPID over 5 days 10 days Every 4 to 6 hours	TAP IR 50 mg (n = 161) TAP IR 75 mg (n = 169) OXY IR 10 (n = 172) PBO (n = 172)	101.2 (95% CI 54.58-147.89) 97.5 (95% CI, 51.81-143.26) 111.9 (95% CI, 66.49-157.38) — Results reported as least squares mean difference from placebo; all p < 0.001
IBU = ibuprofen; IR = immediate release; MS= morphine sulfate; OXY = oxycontin; PBO = placebo; SPI = sum of pain intensity; SPID = sum of pain intensity difference; TAP = tapentadol IR; TOTPAR total pain relief			

Conclusion

Tapentadol IR was recently approved for moderate to severe acute pain in adults. It has dual mechanisms of action as a mu-opioid receptor agonist and norepinephrine reuptake inhibitor. In short-term clinical trials, tapentadol IR has demonstrated efficacy similar to that of various doses of immediate-release oral morphine and oxycodone. Tapentadol IR's place in therapy is unclear, given that there are a number

of opioids to select from (including several generics) when treating acute pain.

Data suggest that tapentadol IR may have a lower incidence of nausea, vomiting and constipation compared to morphine and oxycodone, and, theoretically, other opioids. Other adverse effects appear to be similar to those seen with the opioid class, although tapentadol IR may have some AEs (for example, serotonin syndrome) that are associated with serotonergic drugs. Possible disadvantages of tapentadol IR are: 1) it may need to be taken 4 to 6 times each day to control pain (currently there is no extended-release formulation), 2) its use is limited to patients who can receive enteral medications (currently there is no parenteral formulation), and 3) it is not currently indicated for patients with chronic pain, the population for which a drug with fewer GI effects (especially constipation) may offer a distinct advantage.

A trial of tapentadol IR may be warranted in patients who require an oral opioid for short-term, acute

moderate to severe pain but who suffer from unmanageable, intolerable nausea, vomiting and/or constipation with one of the other agents. Once tapentadol IR hits the market, its place in therapy should become clearer.

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ASSESSMENT QUESTIONS



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1. Which one of the following describes tapentadol IR?
 - a. Mu-opioid receptor antagonist and norepinephrine reuptake inhibitor.
 - b. Mu-opioid receptor antagonist and norepinephrine and serotonin reuptake inhibitor.
 - c. Mu-opioid receptor agonist and norepinephrine reuptake inhibitor.
 - d. Mu-opioid receptor agonist and norepinephrine and serotonin reuptake inhibitor.
2. Which one of the following is tapentadol IR most similar to structurally?
 - a. Morphine.
 - b. Oxycodone.
 - c. Hydrocodone.
 - d. Tramadol.
3. Tapentadol IR is contraindicated in all of the following EXCEPT:
 - a. Patients with acute or severe bronchial asthma or hypercapnia if such patients are in unmonitored settings when resuscitative equipment is unavailable.
 - b. Patients who are elderly.
 - c. Patients with significant respiratory depression.
 - d. Patients with paralytic ileus.
4. Which of the following types of drugs are contraindicated with tapentadol IR?
 - a. Drugs that are metabolized primarily by the cytochrome P450 system.
 - b. Drugs that are primarily renally excreted.
 - c. Drugs that are highly protein bound.
 - d. Monoamine oxidase inhibitors (MAOIs).
5. What should a mother who breast feeds be told about tapentadol IR?
 - a. Tapentadol IR should not be used during breast feeding because it is suspected that the drug is excreted into breast milk, so a risk to the infant cannot be excluded.
 - b. Tapentadol IR should not be used during breast feeding because during clinical trials there were several reports of breast fed infants experiencing respiratory depression while their mothers were taking tapentadol IR.
 - c. It is safe to take tapentadol IR while breast feeding as long as a dose is taken just after the baby finishes feeding.
 - d. It is safe to take tapentadol IR while breast feeding as long as a dose is taken just before the baby's longest sleeping period.
6. Which one of the following occur less frequently with tapentadol IR compared to oxycodone?
 - a. Somnolence.
 - b. Diarrhea.
 - c. Constipation.
 - d. Respiratory depression.
7. How is tapentadol IR administered?
 - a. Intramuscularly.
 - b. Intravenously.
 - c. Orally.
 - d. Subcutaneously.
8. What is the maximum recommended daily dose of tapentadol IR?
 - a. 500 mg on the first day of therapy and 400 mg on subsequent days.
 - b. 700 mg on the first day of therapy and 600 mg on subsequent days.
 - c. 900 mg on the first day of therapy and 800 mg on subsequent days.
 - d. 1.1 g on the first day of therapy and 1 g on subsequent days.
9. How soon may the second dose of tapentadol IR be taken after the first dose?
 - a. One hour after the first dose.
 - b. Two hours after the first dose.
 - c. Four hours after the first dose.
 - d. Six hours after the first dose.
10. The initial dose and frequency of administration should be reduced in which one of the following groups?
 - a. Patients with mild hepatic impairment.
 - b. Patients with moderate hepatic impairment.
 - c. Patients with mild renal impairment.
 - d. Patients with moderate renal impairment.

