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Tramadol Sustained-Release Capsules

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Contents

Abstract

▲ Tramadol is a synthetic, centrally acting analgesic. A sustained-release (SR) capsule formulation of tramadol gradually releases active drug, allowing for twice-daily dosing.

▲ Compared with tramadol SR tablets, tramadol SR capsules produced a smoother plasma concentration profile, with more gradual absorption and lower peak concentrations. There was less intra- and inter-subject variability in tramadol plasma concentrations with SR capsules versus SR tablets.

▲ Tramadol SR capsules had identical bioavailability to tramadol immediate-release (IR) capsules with lower peak concentrations and less fluctuation in plasma concentrations.

▲ Tramadol SR 100mg capsules administered twice daily had equivalent efficacy to tramadol IR 50mg capsules administered four times daily in the treatment of moderate to severe chronic low back pain in a well designed study. Patients receiving tramadol SR capsules were significantly less likely than those receiving tramadol IR capsules to report nausea.

▲ Starting treatment with tramadol SR capsules at a dosage of 50mg twice daily with subsequent dose escalation resulted in improved tolerability in patients with moderate to severe chronic pain.

▲ The lowest tramadol SR capsule dosage of 50mg twice daily (administered to 35% of patients with moderate to severe non-oncological pain) significantly improved pain intensity and frequency in 83.4% and 70.4% of patients, respectively, in a postmarketing observational study evaluating tramadol SR capsules 50–200mg twice daily (n = 3888).

Features and properties of tramadol sustained-release capsules	
Indication	
Treatment of moderate to severe pain	
Mechanism of action	
Centrally acting analgesic	Opioid agonist; inhibits the neuronal reuptake of noradrenaline (norepinephrine) and serotonin
Dosage and administration	
Recommended initial dosage	100–200 mg/day
Recommended maximum dosage	300–400 mg/day
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile (single dose of 50, 100 and 200mg)	
Mean maximum plasma concentration (C_{max}) [μg/L]	70, 137 and 277
Mean time to C_{max} (h)	5.3, 5.9 and 4.9
Mean area under the plasma concentration-time curve from time zero to infinity (μg • h/L)	1039, 2060 and 3952
Mean half-value duration (h)	12.8, 12.9 and 13.0
Mean elimination half-life (h)	6.0, 6.2 and 5.6
Adverse effects	
Most frequent	Nausea, dizziness, vomiting, constipation, somnolence, abdominal pain, headache, dry mouth, dyspepsia, vertigo

The efficacy of tramadol in the treatment of moderate to severe pain is well established.[1] Immediate-release (IR) formulations of the drug achieve maximum plasma concentration (C_{max}) values within 2 hours with an elimination half-life ($t_{½}$) of ≈5–6 hours, necessitating administration four to six times daily.[2] Sustained-release (SR) formulations of tramadol are beneficial in terms of reducing the dosing frequency. In addition, SR formulations of the drug may be associated with a lower incidence of adverse effects related to abrupt peaks in plasma drug concentrations, and a lower incidence of end-of-dose failure (i.e. exacerbations of pain) related to rapidly decreasing post-peak plasma concentrations.[3]

The SR capsule formulation of tramadol[1] contains pellets of ≈1mm diameter.[4] These pellets comprise a membrane controlling the release of active drug and a neutral core that is layered with tramadol hydrochloride.[4] This multiple-units SR pellet formulation may have also have an advantage over single-unit SR tablet formulations of tramadol in terms of producing smoother plasma concentration profiles due to more gradual release of the drug.[3] Tramadol SR capsules are administered twice daily, with the potential for improved patient compliance compared with IR formulations.

This profile provides an overview of the pharmacological properties of tramadol SR capsules, as well as examining their efficacy in patients with moderate to severe chronic pain.

1. Pharmacodynamic Profile

The pharmacodynamic properties of tramadol are well established; this section therefore provides a brief summary based on information reviewed in detail elsewhere.[1,2]

- Tramadol is a synthetic, centrally acting analgesic with a dual mechanism of action.[1] As an opioid agonist, tramadol shows selectivity for the μ-receptor, although its affinity for this receptor is approximately 10 times lower than that of codeine and 6000 times lower than that of morphine (inhibition constants of 2.1, 0.2 and 0.00034 μmol/L).[1] The pharmacologically active *O*-desmethyl (M1) metabolite of tramadol has a 300-fold greater affinity for the μ-receptor than the parent compound.[2] In addition to its opioid agonist activity, tramadol inhibits the neuronal reuptake of noradrenaline (norepinephrine) and serotonin.[1,2]
- Tramadol is a racemic compound.[1,2] It appears that (+)-tramadol is primarily responsible for the inhibition of serotonin reuptake, that (−)-tramadol inhibits noradrenaline reuptake and that (+)-M1 acts as a μ-receptor agonist.[2]
- Tramadol has shown superior analgesic efficacy to placebo in well designed studies in healthy volunteers.[1,2] The M1 metabolite contributes to the analgesic efficacy of tramadol; the efficacy of the drug was lower in individuals deficient in the cytochrome P450 (CYP) isoenzyme CYP2D6 (the isoenzyme responsible for the *O*-demethylation of tramadol) [i.e. poor metabolisers] than in extensive metabolisers.[1]
- Although tramadol influences respiration, it is not likely to cause clinically significant respiratory depression at recommended dosages.[1,2] Tramadol also lacks clinically significant haemodynamic effects and delays gastrointestinal transit to only a minor extent.[1,2]

2. Pharmacokinetic Profile

The pharmacokinetics of tramadol SR capsules were evaluated in healthy volunteers (n = 12–24) in four randomised, open-label, crossover studies.[3-6] Equivalence assessments were made after the reported mean data had undergone logarithmic transformation.[3-5] Equivalence was shown if the 90% confidence interval (CI) of the ratio of pharmacokinetic values for tramadol SR capsules versus the reference drug was within a range of 0.80–1.25.[3-5] Additional data were obtained from the manufacturer's prescribing information.[7]

1 Trade names include Tradonal® Retard, Zamadol® SR caps, Zamudol® LP, Tradonal® SR, Tramadol HCl Meda and Travex®. The use of trade names is for product identification purposes only and does not imply endorsement.

Absorption and Distribution

- Tramadol SR capsules have a mean absolute bioavailability of ≈70%, with a first-pass effect of up to 30%.[7]
- Tramadol SR capsules demonstrated dose linearity across the dose range of 50–200mg.[6] Following administration of single doses of tramadol SR capsules 50, 100 and 200mg, the mean C_{max} was 70, 137 and 277 μg/L; C_{max} was reached (t_{max}) in a mean 5.3, 5.9 and 4.9 hours.[6]
- With single doses of tramadol SR capsules 50, 100 and 200mg, the mean half-value duration (i.e. the time that tramadol plasma concentrations are above half of C_{max}) was 12.8, 12.9 and 13.0 hours, with corresponding values for the mean area under the plasma concentration-time curve from time zero to infinity (AUC_∞) of 1039, 2060 and 3952 μg • h/L.[6]
- Food intake did not affect the pharmacokinetics of tramadol SR 200mg capsules.[4] Bioequivalence in the fasting and nonfasting states was established in terms of C_{max} and AUC_∞ values.
- Although the extent of absorption was slightly lower with a single 200mg dose of the tramadol SR capsule formulation than with a single 200mg dose of a tramadol IR capsule formulation (four 50mg IR capsules) [mean AUC_∞ 5293 vs 5826 μg • h/L], the two formulations were deemed equivalent (point estimate of the SR **:** IR ratio 0.90 [90% CI 0.85, 0.95]).[4] As expected, mean C_{max} values were lower with the SR capsule formulation than with the IR capsule formulation (294 vs 640 μg/L; 0.45 [90% CI 0.43, 0.48]).
- The bioavailability of the tramadol SR and IR capsule formulations was identical at steady state.[5] Volunteers received tramadol SR 100mg capsules at 12-hourly intervals (six doses) or tramadol IR 50mg capsules at 6-hourly intervals (12 doses). The mean AUC from 48 to 72 hours ($AUC_{48–72}$) was 5169 and 5167 μg • h/L with the SR and IR capsule formulations (point estimate of the SR **:** IR ratio 1.00 [90% CI 0.97, 1.03]).
- Less fluctuation in plasma concentrations occurred with the tramadol SR capsule formulation than with the tramadol IR capsule formulation, with mean peak-trough fluctuations between 48 and 72 hours of 58% and 89%, respectively (point estimate of the SR **:** IR ratio 0.66 [90% CI 0.60, 0.72]).[5] Between 48 and 72 hours, mean C_{max} values were 274 and 322 μg/L (0.85 [90% CI 0.81, 0.88]) and mean minimum plasma concentrations were 151 and 136 μg/L (1.12 [90% CI 1.05, 1.19]) with the SR and IR capsule formulations.
- SR capsules produced a smoother tramadol plasma concentration profile than SR tablets, and absorption of tramadol from SR capsules was more gradual.[3] The tramadol SR capsule formulation produced a lower C_{max} (149 vs 183 μg/L; capsule **:** tablet ratio 0.80 [90% CI 0.77, 0.84]), a later t_{max} (5.9 vs 4.9 hours; 1.0 [90% CI 0.5, 1.5]) and a longer half-value duration (13.4 vs 10.4 hours; 1.27 [90% CI 1.17, 1.38]) than the SR tablet formulation.[3] Volunteers received two single doses of tramadol 100mg in the SR capsule and tablet formulations, 5 days apart.
- Intra- and intersubject variability in tramadol plasma concentrations during the initial 2.5 and 3 hours, respectively, following administration was significantly ($p < 0.05$) smaller with tramadol SR capsules than with tramadol SR tablets.[3] This may reflect the fact that the multiple-units SR capsule formulation reaches the upper small intestine (the optimal site of absorption) in a more reproducible manner than single-unit SR tablet formulations, given that the capsule formulation is less dependent on gastric emptying rates.
- Following oral administration, tramadol has an apparent volume of distribution of 203L, with protein binding of 20%.[7] Tramadol crosses the blood-brain barrier and the placenta. Traces of tramadol and its *O*-desmethyl metabolite (0.1% and 0.2% of the original dose) are found in breast milk.

Metabolism and Elimination

- The CYP isoenzymes CYP3A4 and CYP2D6 are involved in the metabolism of tramadol. Metabolism primarily occurs via *N*- and *O*-demethylation, with conjugation of the *O*-demethylation metabolites with glucuronic acid.[7] As previously mentioned,

the *O*-desmethyl (M1) metabolite is pharmacologically active.

- Excretion of tramadol and its metabolites occurs primarily via the kidneys.[7] Following a radiolabelled dose of tramadol, urinary excretion accounted for 90% of the radioactivity.[7] The mean $t_{1/2}$ of tramadol SR capsules following single 50–200mg doses was 5.6–6.2 hours.[6]

Special Patient Populations

- The $t_{1/2}$ of tramadol may be increased 1.4-fold in elderly patients aged >75 years.[7]
- The $t_{1/2}$ of tramadol may also be slightly prolonged in patients with hepatic or renal dysfunction.[7] In patients with liver cirrhosis, $t_{1/2}$ values of 13 and 19 hours have been reported for tramadol and *O*-desmethyltramadol, with values of 22 and 36 hours, respectively, in extreme cases. In patients with renal impairment (creatinine clearance <0.3 L/h [<5 mL/min]), $t_{1/2}$ values were 11 hours for tramadol and 17 hours for *O*-desmethyltramadol, with values of 20 and 43 hours, respectively, in extreme cases.

Potential Drug Interactions

- Drugs that inhibit or induce CYP3A4 or CYP2D6 may affect the pharmacokinetics of tramadol.[1] For example, co-administration of the CYP inducer carbamazepine and tramadol SR capsules resulted in clinically significant reductions in tramadol plasma concentrations.[7]

3. Clinical Efficacy

Compared with Tramadol Immediate-Release Capsules

The efficacy of tramadol SR capsules in patients with moderate to severe chronic low back pain was examined in a randomised, double-blind, double-dummy, parallel-group, multicentre study.[8] Patients received tramadol SR capsules 100mg twice daily (n = 125) or tramadol IR capsules 50mg four times daily (n = 122) for 9 days. Patients were eligible for enrolment if they were aged 18–75 years and had chronic low back pain of ≥3 months duration; the intensity of back pain had to be rated as 30–75mm on a 100mm visual analogue scale (VAS).

The primary efficacy endpoint was the change from baseline in pain intensity (assessed using a 100mm VAS).[8] The pain intensity score at study end comprised the mean of the scores from the early evening assessments conducted over days 5–8. Secondary endpoints included improvement in the quality of sleep (assessed using a validated sleep questionnaire), improvement in functional capacity and patient global assessment of efficacy (statistical analyses were generally not reported for the secondary endpoints).

Tramadol SR capsules were deemed equivalent to tramadol IR capsules if the 90% CI for the between-group difference in the change in pain intensity was within the predefined equivalence range of ±10mm on the VAS.[8] The primary analysis was conducted in the per-protocol population comprising 105 and 99 tramadol SR and IR capsule recipients.

- Tramadol SR capsules had equivalent efficacy to tramadol IR capsules in the treatment of moderate to severe chronic low back pain.[8] According to VAS scores, pain intensity was reduced from baseline by 25.1mm with tramadol SR and 24.7mm with tramadol IR (baseline scores were 53.3 and 55.6mm in the corresponding treatment groups). The between-group difference was 0.45mm (90% CI −4.18, +5.09), confirming the equivalence of the two tramadol formulations.
- Pain intensity progressively decreased up to day 8.[8] Within the first 2 days of therapy, mean VAS pain intensity scores had decreased from baseline to 38.4mm in tramadol SR capsule recipients and 40.6mm in tramadol IR capsule recipients (statistical analysis not reported).
- Both tramadol SR and IR capsules improved the quality of sleep.[8] At baseline, 9.5% of tramadol SR capsule recipients and 7.1% of tramadol IR capsule recipients reported no awakenings due to back pain, compared with 41.0% and 46.9% of patients in the corresponding treatment groups on the last night at

the end of the study. At the final assessment, 29.7% of tramadol SR capsule recipients and 22.2% of tramadol IR capsule recipients were pain free at night.

- Functional capacity improved with both tramadol SR and IR capsules.[8] At the final assessment, >80% of tramadol SR and IR capsule recipients were rated 'without pain' or 'slight pain possible' when putting on a jacket, putting on shoes when seated, and ascending and descending ≥8 steps.
- In terms of global assessment of efficacy, efficacy was rated as good or moderately good by 80.0% of tramadol SR capsule recipients and 80.9% of tramadol IR capsule recipients, with no significant between-group difference (figure 1).[8]

Postmarketing Observational Studies

The efficacy of tramadol SR capsules was also examined in two postmarketing observational studies.[9,10]

In a nonrandomised, open-label, multicentre, postmarketing observational study in outpatients with moderate to severe nonmalignant chronic pain (pain duration of ≥3 months; mean patient age ≈60 years), patients initially received tramadol SR capsules 50mg twice daily with an increase after ≈7 days to a dosage of 100mg twice daily (50mg group; n = 1071) or tramadol SR capsules 100mg twice daily throughout the study (100mg group; n = 854).[9] Patients were followed for 2–3 weeks. The main focus of this study was tolerability (see section 4); however, the change from baseline in pain intensity using a 100mm VAS was also assessed, as was patients' overall assessment of efficacy and concomitant medication use.[9]

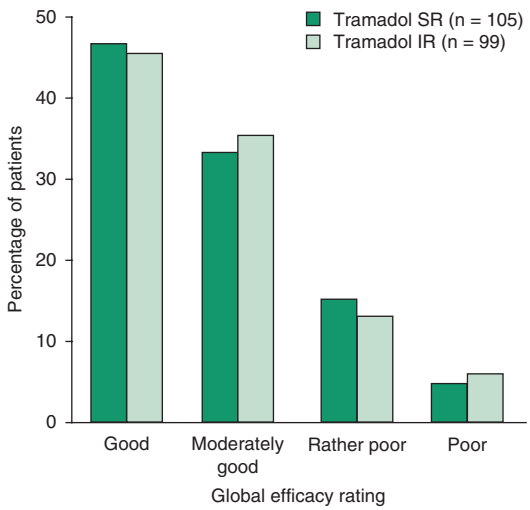

Fig. 1. Patients' global assessment of the efficacy of tramadol sustained-release (SR) capsules in moderate to severe chronic low back pain. In this randomised, double-blind, double-dummy, parallel-group, multicentre study, patients received tramadol SR capsules 100mg twice daily or tramadol immediate-release (IR) capsules 50mg four times daily for 9 days.[8]

- Both tramadol SR capsule regimens reduced pain intensity to a significant extent.[9] Mean VAS scores were reduced from 70.96mm at baseline to 33.66mm at study end in the 50mg group and from 73.73mm at baseline to 35.95mm at study end in the 100mg group (both $p < 0.0001$ vs baseline). There was no significant between-group difference in terms of the improvement in pain intensity. It should be noted that baseline pain intensity scores were significantly higher in the 100mg group than in the 50mg group ($p = 0.001$).
- There were also no significant differences between the 50 and 100mg groups in terms of the proportion of patients interrupting treatment because of insufficient efficacy (0.6% vs 0.5%) or the proportion of patients rating the overall efficacy of treatment as very good (21.3% vs 24.3%), good (53.5% vs 46.1%), fair (19.5% vs 18.0%) or poor (5.7% vs 11.6%).[9]
- Use of concomitant medication, including analgesics, did not significantly differ between the tramadol SR capsule groups.[9] Overall, 68.3% of patients took concomitant medications and 43.8% of patients took analgesics. Similar proportions of patients in the 50 or 100mg groups received concomitant paracetamol (acetaminophen) [17.0% vs 16.9%].

In another postmarketing observational study, 3888 patients with moderate to severe non-oncological chronic pain received tramadol SR capsules 50, 100, 150 or 200mg twice daily for 3 weeks.[10] Osteoarticular disease was present in 88% of patients. This study is reported as an abstract.

- The lowest tramadol SR capsule dosage of 50mg twice daily (administered to 35% of patients) significantly improved pain intensity and frequency ($p < 0.001$ vs baseline) in 83.4% and 70.4% of patients, respectively, receiving this dosage.[10] These improvements were not significantly different to those seen in patients receiving higher dosages of the drug.
- Overall, 92.8% of patients experienced clinical improvement, with significant ($p < 0.001$ vs baseline) reductions in pain intensity and frequency occurring in 85.5% and 71.0% of patients.[10]

4. Tolerability

Data concerning the tolerability of tramadol SR capsules were obtained from a postmarketing observational study in outpatients with moderate to severe nonmalignant chronic pain who received tramadol SR capsules 50mg twice daily with an increase after ≈7 days to a dosage of 100mg twice daily (50mg group; n = 1071) or tramadol SR capsules 100mg twice daily throughout the study (100mg group; n = 854); patients were followed for 2–3 weeks[9] (see section 3 for further study design details). The main objective of this study was to examine the proportion of patients experiencing treatment interruption because of adverse effects (defined as a treatment-emergent adverse event, the causality of which was deemed likely to be due to tramadol or was non-assessable).[9]

- Starting treatment with tramadol SR capsules at a dosage of 50mg twice daily and subsequently increasing the dosage resulted in improved tolerability, compared with initiating treatment at a dosage of 100mg twice daily, in patients with moderate to severe chronic pain.[9]
- Treatment interruption because of adverse effects occurred in significantly fewer patients in the tramadol SR capsule 50mg group than in the 100mg group (5.6% vs 12.6% of patients; $p = 0.001$).[9] Indeed, the risk of treatment cessation because of adverse reactions was 2.3-fold higher in the 100mg group than in the 50mg group. Nausea, dizziness, vomiting and headache were among the adverse effects most likely to cause premature discontinuation and occurred in significantly fewer patients in the 50mg group than in the 100mg group (figure 2).

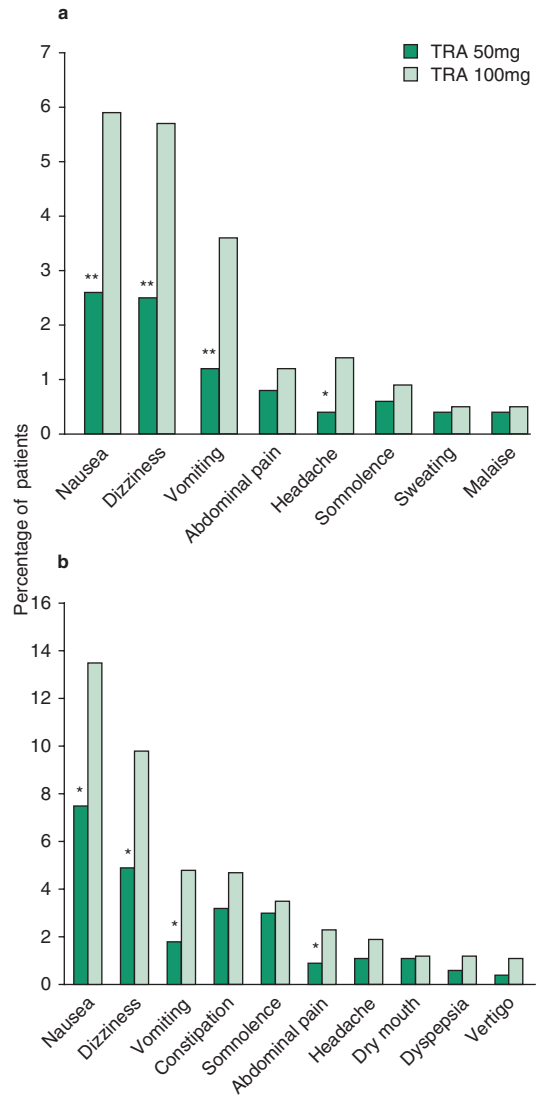

Fig. 2. Adverse effects in outpatients with moderate to severe nonmalignant chronic pain receiving tramadol sustained-release capsules (TRA). In a nonrandomised, open-label, multicentre, postmarketing observational study, patients initially received TRA 50mg twice daily with an increase after ≈7 days to a dosage of 100mg twice daily (n = 1071) or TRA 100mg twice daily throughout the study (n = 854); patients were followed for 2–3 weeks.[9] Depicted are (**a**) the percentage of patients experiencing adverse effects leading to treatment interruption and (**b**) the incidence of adverse effects. * $p < 0.05$, ** $p < 0.001$ vs TRA 100mg.

- Adverse effects occurring in significantly fewer patients in the tramadol SR capsule 50mg group than in the 100mg group included nausea, dizziness, vomiting and abdominal pain (figure 2).[9] The time elapsed until adverse effects occurred was 4.8 and 4.2 days in the corresponding treatment groups ($p = 0.487$); the lack of a significant between-group difference indicates that the dose increase from 50 to 100mg twice daily in the 50mg group was not associated with the occurrence of adverse reactions.[9]
- Patients' overall assessment of tolerability significantly ($p = 0.001$) favoured the tramadol SR capsule 50mg group compared with the 100mg group.[9] Tolerability was rated as very good by 29.4% of the 50mg group versus 25.9% of the 100mg group, good by 54.1% versus 48.1%, fair by 10.1% versus 12.9% and poor by 6.3% versus 13.1%.

The tolerability of tramadol SR capsules was also examined in a 9-day study comparing tramadol SR capsules 100mg twice daily ($n = 125$) with tramadol IR capsules 50mg four times daily ($n = 122$) in patients with moderate to severe chronic low back pain[8] (see section 3 for further study design details).

- In patients with moderate to severe chronic low back pain, nausea was reported by significantly more tramadol IR than tramadol SR capsule recipients (21.3% vs 11.2% of patients; $p = 0.038$).[8] In addition, the intensity of nausea was more severe in tramadol IR than tramadol SR capsule recipients.
- There were no significant between-group differences in the incidence of other commonly reported adverse events such as headache, dizziness, fatigue, sweating, vomiting and pruritus (reported in 5–18% of tramadol SR capsule recipients and 6–29% of tramadol IR capsule recipients; values estimated from graph).[8]
- Withdrawal from the study because of adverse events occurred in 10% of tramadol SR capsule recipients and 8% of tramadol IR capsule recipients.[8] No patients reported serious adverse events and the tolerability of treatment was rated as good or moderately good by 78.2% of tramadol SR capsule recipients and 69.7% of tramadol IR capsule recipients. No clinically relevant laboratory abnormalities were reported in recipients of tramadol SR or IR capsules.

5. Dosage and Administration

According to prescribing information, the initial recommended dosage of tramadol SR capsules is 50–100mg twice daily, administered in the morning and evening without regard to food.[7] The dosage may be titrated to 150–200mg twice daily, depending on the severity of the pain.

Local prescribing information should be consulted for contraindications, precautions, warnings and drug interactions relating to the tramadol SR capsules.

6. Tramadol Sustained-Release Capsules: Current Status

Tramadol SR capsules are approved in numerous countries worldwide for use in the treatment of moderate to severe pain.

Twice-daily administration of tramadol SR capsules is effective in the treatment of moderate to severe chronic pain, providing equivalent analgesia to that afforded by tramadol IR capsules administered four times daily. However, tramadol SR capsules are associated with less nausea than tramadol IR capsules, in line with the lower C_{max} values produced by the SR capsule formulation. It has also been shown that use of a dose-escalation regimen with a starting dosage of tramadol SR capsules 50mg twice daily improves tolerability. Nevertheless, as a large fraction of patients achieve adequate pain relief with tramadol SR capsules 50mg twice daily, a dose increase is not always necessary. Tramadol SR capsules produce smoother, more reproducible plasma concentration profiles than tramadol SR tablets.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on

any comments received were made on the basis of scientific and editorial merit.

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