

## Once-daily tramadol extended-release (Durotram XR) for pain

(tram-a-dol)

### Summary

- Three different formulations of tramadol are now available in Australia: immediate-release, taken every 4–8 hours; sustained-release, taken twice daily; and extended-release, taken once daily.
- Tramadol extended-release (Durotram XR) is a biphasic formulation of tramadol: 25% of the dose is released within 2 hours, while the remaining 75% is gradually released over 24 hours.
- Tramadol extended-release taken once daily has similar efficacy to that of twice-daily tramadol.
- Drug interactions and adverse events limit the role of all tramadol formulations.
- Ensure that patients are aware that tramadol extended-release is a once-daily tablet.
- Advise patients not to take any other product containing tramadol while using tramadol extended-release, without speaking to a doctor or pharmacist.

### PBS listing

#### Restricted benefit

Pain (including pain experienced after dental procedures) where aspirin and/or paracetamol alone are inappropriate or have failed.

Tramadol extended-release is available as 100 mg, 200 mg or 300 mg tablets. Authorities for repeats or quantities greater than 10 tablets will only be granted for severe disabling pain that does not respond to non-opioid analgesics. No repeats will be allowed for prescriptions under the dental listing.

#### Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing tramadol extended-release tablets on a cost-minimisation basis — that is, similar efficacy and cost — compared with tramadol (12-hourly) sustained-release preparations.<sup>1</sup> The PBAC also recommended listing in the dental section with a maximum quantity of 10 tablets with no repeats.<sup>1</sup>

### Place in therapy

Tramadol extended-release (Durotram XR) is a once-daily, biphasic tramadol formulation. The outer layer of the tablet releases 25% of the dose within 2 hours, while the remaining 75% is gradually released from the core over 24 hours.<sup>2,3</sup>

Three different capsule or tablet formulations of tramadol are now available in Australia (Table 1).

**Table 1: Tramadol capsule or tablet formulations available in Australia**

| Formulation                                                                   | Available strengths                  | Dosing frequency |
|-------------------------------------------------------------------------------|--------------------------------------|------------------|
| Immediate-release capsules (Tramadol, Tramal, Tramedo and Zydol)              | 50 mg                                | Every 4–8 hours  |
| Sustained-release tablets (Tramahexal SR, Tramal SR, Tramedo SR and Zydol SR) | 50 mg*<br>100 mg<br>150 mg<br>200 mg | Twice daily      |
| Extended-release tablets (Durotram XR)                                        | 100 mg<br>200 mg<br>300 mg           | Once daily       |

\*Tramal SR is the only sustained-release formulation of tramadol available in the 50 mg strength

Tramadol extended-release taken once daily has similar efficacy to that of twice-daily tramadol. There are some differences in its adverse-event profile, but, like all tramadol formulations, the role of tramadol extended-release is limited by drug interactions and adverse events (see Safety issues).

The PBS listing allows tramadol to be used for up to 10 days. This approach could be considered for indications such as pain after dental extractions, flare-ups in osteoarthritis and for procedural pain.

### Tramadol extended-release is subsidised for short-term use

Tramadol extended-release is PBS subsidised for up to 10 days. Larger quantities of tramadol extended-release can only be prescribed for severely disabling pain that does not respond to non-opioid medications.

No published randomised trial of tramadol extended-release has studied efficacy or safety for more than 12 weeks.

### Tramadol extended-release has similar efficacy to that of tramadol twice daily

Tramadol extended-release once daily has similar efficacy to that of twice-daily tramadol among people with osteoarthritis of the knee.<sup>4</sup> Over 12 weeks, scores on the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain scale improved by almost 60% among people taking tramadol extended-release once daily and among people taking twice-daily tramadol. In this study the median optimal dose in both groups was 200 mg/day.<sup>4</sup>

### Other analgesics should be considered before tramadol

Tramadol is a weak opioid that also inhibits the reuptake of noradrenaline and serotonin.<sup>5</sup>

Paracetamol and an NSAID can be combined when paracetamol alone is inadequate to control mild to moderate pain.<sup>6</sup> Weak opioids are an alternative to adding an NSAID when paracetamol alone is ineffective. Strong opioids are recommended for severe pain or for persistent pain not adequately controlled by weak opioids or NSAIDs.<sup>5-7</sup>

### Do not use tramadol extended-release in people who require rapid titration

Neither tramadol extended-release nor tramadol sustained-release should be used in people who require rapid titration of analgesia to control acute pain or when the level of analgesia required is unpredictable. Less flexibility in dosing and the longer duration of effect make it more difficult to adjust the dose to requirements with these formulations compared with immediate-release tramadol.

### Safety issues

Ensure that the patient is aware that tramadol extended-release should only be taken once daily.

Drug interactions and adverse events limit the role of all tramadol formulations.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website.

### Adverse events are common

The most common adverse events reported in trials of tramadol extended-release include dizziness/vertigo (10% to 26%), nausea (11% to 33%), constipation (10% to 34%) and drowsiness (7% to 30%).<sup>4,8,9</sup>

In trials, up to 81% of people taking tramadol extended-release experienced an adverse event.<sup>4,8,9</sup> A similar proportion of participants (79%) taking tramadol twice daily experienced an adverse event.<sup>4</sup>

Between 8% and 21% of participants receiving tramadol extended-release discontinued treatment because of adverse events.<sup>4,8,9</sup> Similar numbers of people taking tramadol once daily and tramadol twice daily discontinued because of adverse events.<sup>4</sup>

Adverse events can appear within days of starting tramadol extended-release (Table 2).<sup>4</sup>

**Table 2: Time to onset of common adverse events in a clinical trial<sup>4</sup>**

| Adverse event     | Patients experiencing event | Median time to onset |
|-------------------|-----------------------------|----------------------|
| Nausea            | 32%                         | 6 days               |
| Dizziness/vertigo | 26%                         | 4 days               |
| Constipation      | 33%                         | 9.5 days             |
| Drowsiness        | 30%                         | 3 days               |

As with other opioids, the prevalence of adverse events increases with dosage. In one study, 12% of participants taking 100 mg tramadol extended-release discontinued due to adverse events. This rose to 18% in those taking 200 mg/day and to 32% in those taking 300 mg/day. The rate of discontinuation due to adverse events was 7% in the placebo group.<sup>8</sup>

### Less dizziness or vertigo but more drowsiness among people using tramadol extended-release

Dizziness or vertigo is less common in people taking tramadol extended-release once daily than in those taking tramadol sustained-release twice daily (26% vs 37%,  $p = 0.017$ ).<sup>4</sup> However, drowsiness is more common among those taking a once-daily dose than among those taking tramadol twice daily (30% vs 21%,  $p = 0.047$ ).<sup>4</sup> The prevalence of nausea, constipation, headache, vomiting and weakness is similar in both groups, although vomiting was reported to be less severe among people taking once-daily tramadol.<sup>4</sup>

### Adverse events and drug interactions limit the role of tramadol formulations

As for all tramadol formulations, tramadol extended-release:

- is contraindicated in people using monoamine oxidase inhibitors (MAOIs), including moclobemide. Do not use tramadol during or within 14 days of MAOI use.<sup>5,7,10</sup>
- should be used with caution in people with severe renal impairment (creatinine clearance  $< 30$  mL/min), as it and its metabolites are primarily renally excreted. There have been no studies of tramadol extended-release in people with severe renal impairment.
- should be used with caution in people with severe

hepatic impairment, as it is extensively metabolised in the liver.

- should be used with caution in people with epilepsy or at risk of seizures, and when combined with other drugs that lower the seizure threshold (such as tricyclic antidepressants).<sup>5,7,10</sup>
- interacts with serotonergic drugs (e.g. selective serotonin reuptake inhibitors, mirtazapine, venlafaxine, duloxetine, selegiline, St John's wort) and may cause serotonin toxicity.<sup>5,7,10</sup> Ask which medications, including complementary and over-the-counter medicines, a patient is taking.
- may interact with warfarin.<sup>11</sup> Monitor International Normalised Ratio (INR) when tramadol is started in people taking warfarin, particularly during the first 7 days.

### Dosing issues

The recommended starting dose of tramadol extended-release is 100 mg once daily.<sup>10</sup> If this is insufficient to control pain, increase the dose to 200 mg after 2 full days of treatment (i.e. on day 3 of therapy).<sup>12</sup> This may be done by taking two 100 mg tablets at the same time.

The correct dose is the lowest dose that controls pain for 24 hours without intolerable side effects. After titration, the most common dose is 200 mg once daily.<sup>4</sup> However, if this is still insufficient to control pain, the dose can be further increased every 2 days in 100 mg increments up to a maximum of 400 mg daily.<sup>10,12</sup> Manage incident pain during the titration period with paracetamol or an NSAID.<sup>12</sup>

The tablets must be swallowed whole and should not be broken, crushed or chewed.

### Ensure patients do not confuse the extended-release and sustained-release formulations

Tramadol extended-release (Durotram XR) is designed to be taken once a day. The sustained-release formulations (Tramal SR, Tramahexal SR, Tramedo SR and Zydol SR) are designed to be taken twice a day.

Reinforce that tramadol extended-release is a once-daily dose — particularly when prescribing to people who have previously taken immediate-release or sustained-release formulations of tramadol. Warn people that taking more than one dose a day

could increase their risk of seizures or other adverse events — particularly if the maximum recommended dose of 400 mg/day is exceeded.

### Advise people to take tramadol extended-release in a consistent manner

While tramadol extended-release can be taken with or without food, advise people to take their medication in the same manner each day (i.e. always with food or always without food) to ensure a consistent analgesic effect. Consuming a high-fat meal immediately before taking tramadol extended-release can increase the maximum plasma concentration of tramadol by 54% but does not significantly impact upon the overall extent of absorption.<sup>10</sup>

### Information for patients

Advise patients as follows.

- Take tramadol extended-release once a day. If possible, it may be best to take it in the evening, as it can cause drowsiness.

- Do not take any other product containing tramadol while using tramadol extended-release, without speaking to a doctor or pharmacist.
- Swallow the tablet whole at the same time each day.
- Adverse events are common and include dizziness, nausea, constipation and drowsiness.
- Check with your doctor or pharmacist before using any prescription medicines or over-the-counter medicines (including herbal preparations) while taking tramadol, as interactions may occur.

Discuss the Durotram XR consumer medicine information (CMI) leaflet (available at [www.nps.org.au](http://www.nps.org.au)).

### Medicine Update

An NPS *Medicine Update* leaflet on tramadol is available for consumers at [www.nps.org.au](http://www.nps.org.au).

*Medicine Update* helps consumers to ask the right questions about new medicines, and helps them compare the potential benefits and harms of a new medicine with those of other medicines.

### References

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