

NEW DRUG EVALUATION

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TRAMACET®

Tramacet® is a fixed dose combination analgesic, with each tablet containing tramadol 37.5 mg and paracetamol 325 mg. It is licensed for the treatment of moderate to severe pain. This combination is no more effective than ibuprofen in acute pain and no more effective than codeine plus paracetamol in post-surgical and chronic pain. Common adverse effects include nausea, dizziness and somnolence. In clinical practice, the tramadol/paracetamol combination offers patients little advantage in terms of efficacy, adverse effects or convenience compared with current standard analgesics and its use is therefore not currently recommended.

What is it?

Tramacet® (Janssen-Cilag) is a fixed dose combination analgesic containing tramadol 37.5 mg and paracetamol 325 mg per tablet. It is licensed for the symptomatic treatment of moderate to severe pain.¹ The recommended dose is 2 tablets initially, with additional doses taken at six hourly intervals, to a maximum of 8 tablets per day (equivalent to 300 mg tramadol and 2600 mg paracetamol).¹

How effective is it?

Acute pain

In acute pain following tooth extraction a combined analysis of three single-dose comparative double-blind trials (n=1197) showed that 2 tramadol/paracetamol 37.5/325 mg tablets provided greater pain relief than tramadol 75 mg or paracetamol 650 mg alone over an 8 hour period but was no more effective than ibuprofen 400 mg.²

A second meta-analysis of 1376 patients with dental pain showed that the number of patients who needed to be treated for 1 patient to obtain a 50% reduction in pain 8 hours after a single dose of analgesia was 3 patients for ibuprofen 400mg, 3 patients for tramadol/paracetamol 75/650 mg combination, 5 patients for paracetamol 650 mg alone and 10 patients for tramadol 75 mg alone.^{3,4}

A single dose trial (n=456) after tooth extraction compared tramadol/paracetamol (75/650 mg) to tramadol 100 mg.⁵ The tramadol/paracetamol combination was superior to tramadol on all primary efficacy endpoints over a 6 hour period. However, trials after gynaecological surgery (n=200) and after orthopaedic surgery (n=200) showed that a single dose of tramadol/paracetamol 112.5/975 mg combination (higher strength than the single marketed dose) was no more effective than tramadol 112.5 mg alone.⁶ The combination was only statistically superior to paracetamol 975 mg alone at 5-8 hours post-dose.⁶ This is to be expected because paracetamol has a shorter half-life than tramadol.

In postsurgical pain following abdominal or orthopaedic surgery a 6 day double-blind, randomised, active- and placebo- controlled trial (n=305) did not show that tramadol/paracetamol 37.5/325 mg provided better pain relief than codeine/paracetamol 30/300 mg during the first 4

hours after the first dose of study medication.⁷ No statistical differences were reported between the two active treatment groups in average daily pain intensity scores and average daily pain relief scores on days 1 to 6.

No trials have been published comparing tramadol/paracetamol with full doses of paracetamol (1g).

Chronic pain

In a 4 week comparative double-blind randomised study in adults (n=462) with chronic non-malignant low back pain, osteoarthritic pain, or both, tramadol/paracetamol 37.5/325 mg had comparable efficacy to codeine/paracetamol 30/300 mg.⁸ The use of supplemental analgesia (ibuprofen 400 mg) was similar for both treatments.

A number of randomised placebo-controlled trials have evaluated the use of tramadol/paracetamol in a variety of chronic pain conditions (lower back pain, osteoarthritis and fibromyalgia).⁹⁻¹³ The tramadol/paracetamol combination was shown to give superior pain relief compared to placebo, as would be expected. It cannot be determined from the results of the placebo controlled studies whether the improvement seen with tramadol/paracetamol is due to the combination or solely attributable to the paracetamol component because there was no paracetamol control arm. No trials were found comparing tramadol/paracetamol with each component used alone in patients with chronic pain.

How safe is it?

The adverse effect profile of tramadol has been reviewed in a previous Drug Update.¹⁴

Adverse effects were more common with tramadol (37.1% of patients) and tramadol/paracetamol (35.8%) than with paracetamol (15.9%) or ibuprofen (12.1%) in single dose trials.¹⁵ Nausea, vomiting, dizziness and somnolence were most prominent in the tramadol groups. Adding paracetamol to tramadol did not appear to affect the incidence of adverse effects reported.

In a comparative study, the incidence of constipation was significantly lower in the tramadol/paracetamol group than in the codeine/paracetamol group (35/309 vs. 32/153, p<0.01); however, withdrawal rates due to adverse events were similar (12% vs. 14%).⁸

Tramadol has a greater potential for drug interactions than codeine. It should not be prescribed concomitantly with selective and non-selective MAO inhibitors.¹ Caution is advised in patients taking selective serotonin re-uptake inhibitors and tricyclic antidepressants, since concomitant use may increase the risk of seizure and serotonin syndrome.¹ There have been reports of tramadol increasing the prothrombin time in patients taking warfarin.¹ Carbamazepine and other enzyme inducers may reduce the efficacy of tramadol.¹

What other options are there?

If patients are receiving maximum doses of regular paracetamol and additional pain relief is required then supplemental doses of either a non-steroidal anti-inflammatory drug such as ibuprofen or an appropriate dose

of a less toxic opioid such as codeine or dihydrocodeine may be helpful. Combined preparations should not normally be used because they contain too small a dose of opioid, do not allow for dose titration and may be expensive.

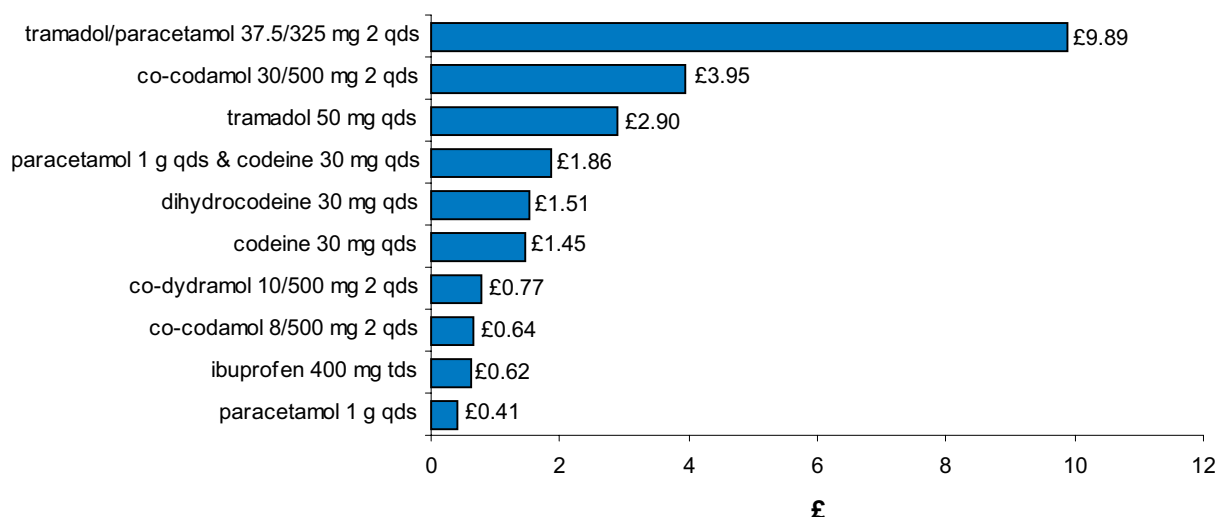
When should it be used?

The tramadol/paracetamol 37.5/325 mg combination is slightly more effective than paracetamol 650mg alone but no more effective than ibuprofen 400mg in acute pain and no more effective than codeine/paracetamol (30/300) in post-surgical and chronic pain.

In clinical practice, the tramadol/paracetamol combination offers patients little advantage in terms of efficacy, adverse effects or convenience over current standard analgesics. Therefore, the prescribing of tramadol/paracetamol combination tablets is not currently recommended.

How much does it cost?

Cost for 7 days treatment (prices from MIMS/Drug Tariff July 2004)



NB. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, A- abstract, E-editorial

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