

**tramadol 37.5mg/paracetamol 325mg tablet (Tramacet<sup>o</sup>)**

**Janssen-Cilag**

**No. (236/06)**

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**Tramadol 37.5mg/paracetamol 325mg tablet (Tramacet<sup>o</sup>)** is not recommended for use within NHS Scotland for the symptomatic treatment of moderate to severe pain.

Tramacet had similar efficacy to another combination analgesic in clinical studies, though the dose of paracetamol in the other analgesic preparation was lower than that usually used in the UK. Tramacet costs significantly more than its individual components prescribed separately.

Overleaf is the detailed advice on this product.

**Chairman  
Scottish Medicines Consortium**

**Tramadol 37.5mg /  
Paracetamol 325mg tablet  
(Tramacet<sup>o</sup>)**

**Indication**

Symptomatic treatment of moderate to severe pain

**Dosing information**

Initial dose: 2 tablets. Additional doses can be taken as needed, not exceeding 8 tablets per day. The dose should be individually adjusted according to pain intensity and response of the patient.

**UK launch date**

May 2004

**Comparator medications**

Co-codamol, tramadol, ibuprofen, paracetamol and codeine

**Cost of relevant comparators**

Drug	Regimen	Cost per week (£)
Tramacet	2 tablets four times a day	9.40
Co-codamol (30/500)	2 tablets four times a day	4.48
Paracetamol + codeine	Paracetamol 1g + codeine 60mg four times a day	3.85
Paracetamol + tramadol	Paracetamol 1g + tramadol 100mg four times a day	3.52
Paracetamol + tramadol	Paracetamol 1g + tramadol 50mg four times a day	2.07
Ibuprofen	400mg three times a day	0.58

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

**Summary of evidence on comparative efficacy**

Two studies have compared Tramacet with co-codamol in post-surgical and chronic pain, chronic non-malignant low back pain and osteoarthritis or both. The first study was a multi-centre, randomised double-blind, active and placebo-controlled trial which compared Tramacet with co-codamol (30/300) and placebo in patients who had undergone a therapeutic arthroscopic procedure of the knee or shoulder or abdominal surgery for inguinal or ventral hernia. Patients had a score = 40mm on a pain visual analogue scale (VAS); 0-100mm where 0=no pain and 100=extreme pain. Exclusion criteria included previous failure with tramadol and inability to tolerate tramadol. Patients were randomised to Tramacet, co-codamol or placebo; 2 tablets initially on day 1 after surgery, followed by 1-2 tablets four times a day as needed for pain for 6 days. The primary efficacy variables were total pain relief (TOTPAR), sum of pain intensity differences (SPID) and sum of pain relief and pain intensity differences (SPRID) during the first 4 hours after the first dose of study medication on day 1. Pain intensity was ranked on a 4 point Likert scale and pain relief measured using a 6 point Likert scale. The study was not powered to compare active treatments.

The number of patients included in the intention-to-treat population was 305. Both Tramacet and co-codamol were significantly superior to placebo for the primary outcome measures. There were no statistically significant differences between Tramacet and co-codamol for the primary outcome measures.

The second study compared the efficacy and tolerability of Tramacet and co-codamol in 462 patients with chronic non-malignant pain (low back pain or osteoarthritis of any joint or both). The 4 week randomised double-blind, parallel-group, active control, double dummy, multi-centre trial, randomised patients in a 2:1 ratio to Tramacet or co-codamol (30/300) and excluded patients with a history of seizures, and those taking monoamine oxidase inhibitors, tricyclic antidepressants or other drugs that may reduce the seizure threshold. Patients were instructed to take 1 or 2 tablets every 4-6 hours as needed for pain up to a maximum of 10 tablets per day (8 tablets in patients >75 years). Both treatment groups had similar results for all outcome measures, which included SPID, TOTPAR, pain relief and intensity difference (PRID) and patient and physician global assessments.

Two studies compared Tramacet with tramadol in postoperative dental pain and sub-acute low back pain. The first study recruited 456 patients aged between 18 and 75 years who underwent surgery for at least two upper or lower impacted third molars. They were required to have moderate or severe pain (assessed on a 4 point Likert scale) and  $\geq 50$ mm on a 100mm VAS within 5 hours after surgery. Exclusion criteria included previous tramadol or Tramacet failure and NSAID use in the previous three days. Patients received either Tramacet 75mg/650mg, tramadol 100mg or placebo as a single-dose. Rescue medication (other than tramadol or paracetamol) could be taken. Pain intensity and pain relief were reported on a 4 point and 5 point Likert scale respectively, at 30 minutes, and then 1, 2, 3, 4, 5, and 6 hours after the dose of the study medication. Values for TOTPAR, SPID and SPRID were obtained and were considered the primary efficacy endpoints. At the final assessment patients also gave an overall rating for the study medication on a 5 point Likert scale. For all efficacy endpoints Tramacet was superior to tramadol or placebo ( $p < 0.001$ ). Forty seven percent of patients in the Tramacet group and 17% and 5% in the tramadol and placebo groups respectively rated the study medication as excellent, very good or good overall.

Other data were also assessed but remain commercially confidential.\*

A meta-analysis of seven randomised double-blind trials compared single-dose Tramacet with ibuprofen, tramadol, paracetamol and placebo in patients with moderate to severe postoperative pain. The focus of the analysis was on the five trials involving dental pain as these data gave reliable estimates of analgesic efficacy. The number needed to treat (NNT) for at least 50% pain relief was 2.6 (95% confidence interval (CI) 2.3-3.0) for Tramacet (75mg/650mg) compared with placebo over 6 hours. The NNTs for tramadol 75mg, paracetamol 650mg and ibuprofen were 9.9 (95% CI 6.9-17), 3.6 (95% CI 3.0-4.5) and 2.3 (95% CI 2.0-2.6) respectively. The authors concluded that the superiority of Tramacet over its individual components had been demonstrated.

A number of studies have shown that Tramacet is superior to placebo for pain relief in patients with low back pain or fibromyalgia, as well as in osteoarthritis (OA), as add-on therapy in patients receiving a non steroidal anti-inflammatory drug or selective inhibitor of cyclo-oxygenase-2 (COX-2) inhibitor, for flare or inadequately controlled OA pain.

## Summary of evidence on comparative safety

In the studies involving Tramacet and co-codamol, treatment-emergent adverse effects with an incidence of = 4.5% included nausea, dizziness, vomiting, headache, somnolence and constipation. In the first study constipation occurred less often with Tramacet than with co-codamol and rates of dizziness and somnolence were higher for Tramacet compared with co-codamol. In the second study rates of somnolence and constipation were significantly higher in the co-codamol groups compared with the Tramacet group ( $p < 0.05$ ). A similar range of adverse effects was observed in the studies comparing Tramacet with tramadol. Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. The summary of product characteristics warns that patients with epilepsy controlled by treatment or patients susceptible to seizures should be treated with Tramacet only if there are compelling circumstances.

## Summary of clinical effectiveness issues

The paracetamol content of Tramacet is 325mg and therefore less than the standard dose of paracetamol prescribed in the UK. In addition, there are no trials comparing Tramacet to the strength of co-codamol generally used in the UK (codeine 30mg/paracetamol 500mg).

The value of compound analgesics containing a simple analgesic and an opioid has been questioned. The British National Formulary (edition 50; September 2005) states that compound analgesic preparations reduce the scope for effective titration of the individual components in the management of pain of varying intensity.

## Summary of comparative health economic evidence

The manufacturer provided a decision tree model to show the cost-effectiveness of Tramacet compared to co-codamol (30/300mg) or tramadol for patients with chronic pain. Since there was no clinical trial that compared the three treatments directly, the economic model used data from the randomised control trial of patients with chronic low back pain or osteoarthritis and an unpublished study in sub-acute low back pain to compare the treatments indirectly. The economic model used 'patient satisfaction' as a proxy for successful pain control and took account of constipation and other side effects of treatment. The modelling was carried out for a one-month time horizon. Utility values were taken from a published conjoint analysis study conducted in patients with cancer and non-cancer pain. Resource use was estimated by assumptions verified by a clinical expert.

The ICER of Tramacet over co-codamol is £8000 per QALY. Tramadol was not considered an effective treatment option being more expensive and less effective than co-codamol and hence ruled out by dominance.

The economic model contained a number of weaknesses. Although provided to support the prescribing of Tramacet in patients with moderate to severe pain, much of the evidence used to populate the model was derived from a patient population with only mild to moderate pain. In addition, the economic analysis compares Tramacet to a co-codamol formulation with a lower dose of paracetamol than is used in the UK. The analysis does not compare the use of Tramacet to its individual components taken separately, where the acquisition costs appear considerably lower. It must also be noted that the economic case does not provide any

support for the use of Tramacet in acute pain as the analysis was focused specifically on chronic pain studies.

## **Patient and public involvement**

A Patient Interest Group submission was not made.

## **Budget impact**

The company estimated that the net drug budget impact from the introduction of Tramacet would be £10,300 in the first year and £15,900 in the fifth year on the basis of restricting the use of Tramacet to patients who have failed treatment with either tramadol or co-codamol.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 15 December 2005.*

*Drug prices are those available at the time the papers were issued to SMC for consideration.*

*\* Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

*The undernoted references were supplied with the submission.*

*Smith AB, Ravikumar TS, Kamin M, Jordan D, Xiang J, Rosenthal N (2004). Combination tramadol plus acetaminophen for postsurgical pain. *The American Journal of Surgery* 187, 521-527*

*Mullican WS, Lacy JR (2001) Tramadol/Acetaminophen Combination Tablets and Codeine/Acetaminophen Combination Capsules for the Management of Chronic Pain: A Comparative Trial. *Clinical Therapeutics* 23 9: 1429-1445*

*Fricke JR, Hewitt DJ, Jordan DM, Fisher A, Rosenthal NR (2004). A double-blind placebo controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain. *Pain* 109: 250-257*

*Edwards JE, McQuay HJ, Moore RA (2002). Combination Analgesic Efficacy: Individual Patient Data Meta-Analysis of Single-Dose Oral Tramadol Plus Acetaminophen in Acute Postoperative Pain. *Journal of Pain and Symptom Management* 23 2: 121-130*