

Tramacet (tramadol/paracetamol)

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- *Tramacet* is a compound analgesic comprising tramadol (37.5mg), a weak synthetic centrally acting opioid analgesic, and paracetamol (325mg), a non-opioid and non-salicylate analgesic. It is indicated for the treatment of moderate to severe pain.
- The results of two studies suggest that *Tramacet* has similar efficacy to co-codamol (US strength 30mg/300mg). One study included 306 patients who had undergone arthroscopy or abdominal surgery, and the other 452 patients with chronic non-malignant pain.
- A meta-analysis involving 1376 patients found single dose *Tramacet* to be more effective than its individual components alone and to have similar efficacy to ibuprofen for acute pain.
- *Tramacet* had a similar range and incidence of side effects as co-codamol (30mg/300mg) in published studies. These included nausea, dizziness, vomiting, headache, somnolence and constipation. However, use of *Tramacet* was associated with a lower incidence of constipation and possibly somnolence. Tramadol monotherapy has been associated with a number of other reactions; these include convulsions, hallucinations and allergic reactions. Tramadol has the potential for a number of drug interactions.
- *Tramacet* is more than twice the price of UK strength co-codamol (30mg/500mg), an established compound analgesic. As published studies have shown *Tramacet* to be no more effective than co-codamol (30mg/300mg) or ibuprofen its use cannot be recommended.

Introduction

Pain is multifactorial and involves both central and peripheral mechanisms. Control of pain can be difficult to achieve with a single drug without causing significant adverse effects. Using two drugs with complementary mechanisms of action targets more than one pain pathway and may enhance analgesia while minimising adverse effects.¹

Tramacet is a combination analgesic, containing 37.5mg tramadol and 325mg paracetamol, which has recently been launched for the treatment of moderate to severe pain.

Tramadol is a synthetic, centrally acting opioid analgesic that has a weak action on μ -opioid receptors (6000 times weaker than morphine)¹ and additionally inhibits reuptake of noradrenaline and enhances serotonin release within central pain pathways.² Paracetamol is a non-opioid, non-salicylate analgesic with an unclear mechanism of action. It appears to have some central actions including inhibition of N-methyl-D-aspartate, substance P mediated nitric oxide synthesis and release of prostaglandin E₂.¹

Evidence

Tramacet has been studied in a number of randomised controlled trials (RCTs) for the treatment of acute and chronic pain (see Appendix II for further details). A number of studies have shown *Tramacet* to be superior to placebo for pain relief in patients with chronic lower back pain³ and fibromyalgia.⁴ Active comparator studies are outlined below.

One such study, a multicentre RCT involved 306 patients (mean age 47.3 years) who had undergone either arthroscopy of the knee or shoulder, or abdominal surgery for inguinal or ventral hernia.⁵ All patients had moderate postsurgical pain (≥ 40 mm on a 0-100mm pain visual analogue scale). Patients were excluded if they had previously failed or could not tolerate tramadol therapy.

Study participants were randomised to *Tramacet*, co-codamol (US strength - 30mg/300mg) or placebo two tablets initially, then one or two tablets four hourly as necessary (maximum of 8/24 hours). The main outcome measures were total pain relief, sum of pain

Brand Name, (Manufacturer): *Tramacet* (Janssen-Cilag)

BNF Therapeutic Class: 4.7.1 Non-opioid analgesics, compound analgesic preparations.

Licensed Indications: *Tramacet* tablets are indicated for the symptomatic treatment of moderate to severe pain.

Dosage and Administration: Initially, two tablets, followed by further doses at intervals of six hours or more to a maximum of eight tablets in 24 hours (300mg tramadol and 2600mg paracetamol). *Tramacet* should not be administered for longer than is strictly necessary. If repeated use or long-term treatment is required, then regular monitoring should take place (with breaks in treatment, where possible), to assess whether continuation of the treatment is necessary.

Marketed: May 2004

Cost Comparisons: MIMS August 2004 – 28 days treatment



N.B. Doses shown for general comparison and do not imply therapeutic equivalence

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intensity differences and sum of pain relief and pain intensity differences during the four hours after the first dose of study medication.

There were no significant differences between the two active treatments for any of the main outcome measures; both were superior to placebo. *Tramacet* was statistically significantly better than placebo at reducing the secondary outcome measures of average daily pain relief scores and average daily pain intensity scores; co-codamol (30mg/300mg) was not. Overall medication assessment was rated as good or very good by 68.8% and 61.5% of patients on *Tramacet* and co-codamol (30mg/300mg), respectively, compared to 46.4% of patients on placebo.

Another RCT enrolled 462 patients with chronic non-malignant pain (back pain and/or osteoarthritis) from 58 US centres.⁶ Subjects were randomised in a 2:1 ratio to *Tramacet* or co-codamol (30mg/300mg) one or two tablets every four to six hours (maximum 10/24hrs). Both treatment groups had similar results for all outcome measures, which included pain relief, change in pain intensity, total pain relief scores and patient and physician global assessments.

In a meta-analysis of seven unpublished RCTs involving 1783 patients with acute pain (dental, gynaecological or orthopaedic) the efficacy of a single dose of *Tramacet* (two or three tablets) was compared to either component alone or ibuprofen (400mg).⁷ Due to limited data, the analysis concentrated on the 1376 dental patients. The number needed to treat (NNT) for one patient to achieve at least 50% pain relief was about 3 for *Tramacet* and 2 for ibuprofen, but for the individual components, paracetamol and tramadol, NNTs were around 8 and 12, respectively.

Tramacet has also been studied as add-on therapy for osteoarthritis (OA) flare. 307 patients (40-75 years) on COX-2 inhibitors with symptomatic OA of a knee or hip joint and moderate pain (≥ 50 mm on a 0-100mm visual analogue scale) were randomised to *Tramacet* or placebo.⁸

Tramacet was statistically significantly more effective than

placebo for pain-related outcomes (improvement in visual analogue score and final pain relief rating score) and for both patient and physician global assessments. However, *Tramacet* was only superior to placebo for the physical function component of the Western Ontario and McMaster Universities (WOMAC) OA score but not for the pain or stiffness components. Similarly, *Tramacet* was superior to placebo for the physical component of the Quality of Life Short-Form-36 (SF36) score but not the other components, which included bodily pain, general health, vitality and mental health.

Safety

In the two studies comparing *Tramacet* with co-codamol (30mg/300mg), discontinuation rates due to side effects were similar in both groups.^{5,6} Side effects were also similar and included nausea, dizziness, vomiting, headache, somnolence and constipation. In one study, patients assigned to co-codamol (30mg/300mg) had a greater incidence of constipation ($p < 0.01$) and somnolence ($p = 0.05$).⁶

The Committee on Safety of Medicines has highlighted a number of concerns about adverse effects associated with tramadol including the occurrence of withdrawal reactions, and the potential to cause dependence and convulsions.² Such adverse reactions have generally been associated with doses of tramadol higher than those likely to be administered using *Tramacet*, or have occurred in at-risk patients. Although none of the above studies reported serious reactions, exclusion criteria variously included a history of drug/alcohol abuse or seizures, and the concurrent use of medication that might reduce seizure threshold. *Tramacet* should not be used in patients with epilepsy unless there are compelling reasons.

Place in Therapy

Compound analgesics are indicated for the treatment of moderate pain. Although the BNF notes that compound analgesics have several limitations including the lack of scope for effective titration of the individual components for pain that varies in intensity, they are widely used in practice.⁹ Available preparations include co-codamol,

co-proxamol and co-dydramol. *Tramacet*, a new compound analgesic will compete with these products.

Compared to US strength co-codamol (30mg/300mg), *Tramacet* has demonstrated similar efficacy; however, in one study patients who had previously failed tramadol were excluded. *Tramacet* has not been compared to UK strength co-codamol (30mg/500mg), which contains a higher dose of paracetamol and, on theoretical grounds, may provide more effective pain relief. *Tramacet* has also not been compared to full dose paracetamol (1g). Single dose studies indicate similar efficacy to ibuprofen.⁷

Tramacet costs twice as much as generic UK co-codamol (30mg/500mg) and is twenty times the cost of ibuprofen or paracetamol. *Tramacet* cannot be recommended as it has not been shown to be more effective than co-codamol (30mg/300mg) and ibuprofen, and has a greater number of restrictions and precautions associated with its use.

Key Papers

5. Smith AB, Ravikumar TS, Kamin M et al. Am J Surg 2004; **187**: 521-7
6. Mullican WS, Lacy JR. Clin Ther 2001; **23**: 1429-45
8. Emkey R, Rosenthal N, Wu S-C et al. J Rheumatol 2004; **31**: 150-6

Appendix I: Bibliography Appendix II: Table of Clinical Trials

Risk Management Issues:

Unlike other compound paracetamol-containing analgesics, *Tramacet* does not have an official co-name. A lack of indication of its paracetamol content could potentially increase the risk of overdose by use of additional paracetamol. The similarity between the brand name, *Tramacet* and the generic name tramadol may also constitute a risk when picking from drug dictionaries or dispensary shelves.

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Appendix I

Bibliography

References

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2. CSM/MCA. Tramadol – (Zydol, Tramake and Zamadol). *Current Problems in Pharmacovigilance* 1996; **22**: 11
3. Ruoff GE, Rosenthal N, Jordan D et al. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin Ther* 2003; **23**: 1123-41
4. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *Am J Med* 2003; **114**: 537-45
5. Smith AB, Ravikumar TS, Kamin M et al. Combination tramadol plus acetaminophen for postsurgical pain. *Am J Surg* 2004; **187**: 521-7
6. Mullican WS, Lacy JR. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: a comparative trial. *Clin Ther* 2001; **23**: 1429-45
7. McQuay H and Edwards J. Meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. *Eur J Anaesthesiol* 2003; **20** (suppl 28): 19-22
8. Emkey R, Rosenthal N, Wu S-C et al. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2004; **31**: 150-6
9. Chapter 4.7.1 Non-opioid analgesics. BNF edition 47, 2004. The Pharmaceutical Press.

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Appendix II

Table 1: Summary of published randomised controlled trials of *Tramacet*

RefNo	Trial Design	Trial Population	Treatment	Outcomes	Results
Active comparators					
5	<p>RCT – multicentre, USA, double-blind, active and placebo controlled</p> <p>No power statement included in published paper.</p>	<p>306 patients randomised, 305 in intention to treat analysis. Patients (18-79 years, mean 47.3 years) had undergone either arthroscopic procedure of knee or shoulder or abdominal surgery for inguinal or ventral hernia and had to have moderate postsurgical pain, defined as ≥ 40mm on pain visual analogue scale (PVA – 0 to 100mm) and intensity of at least 2 on a 4 point pain intensity scale (0=none, 3=severe).</p> <p>Exclusion criteria included:</p> <ul style="list-style-type: none"> • Use of analgesics within 3 hrs • Concomitant use of sedatives • Antiemetics or steroid injections on day of surgery • Long-acting nerve blocks • Inability to tolerate tramadol • Previous failed treatment with tramadol • Treatment with antipsychotic medication • Tramadol use within 30 days 	<ul style="list-style-type: none"> • <i>Tramacet</i> • Co-codamol (30mg/300mg) • Placebo • All given as two tablets initially then one or two tablets four times a day (max 8/24 hours) 	<p>Primary:</p> <ul style="list-style-type: none"> • Total pain relief (TOTPAR), sum of pain intensity differences (SPID) and sum of pain relief and pain intensity differences (SPRID) during 4 hours after first dose of study medication 	<ul style="list-style-type: none"> • <i>Tramacet</i> was more effective than placebo for: <ul style="list-style-type: none"> ➢ TOTPAR 6.5 vs. 4.5, respectively, p=0.004 ➢ SPID 2.7 vs. 2.0 p=0.015 ➢ SPRID 9.2 vs. 6.6 p=0.005 • Co-codamol was more effective than placebo: <ul style="list-style-type: none"> ➢ TOTPAR 5.8 vs. 4.5, p=0.052 ➢ SPID 2.7 vs. 2.0, p=0.019 ➢ SPRID 8.5 vs. 6.6, p=0.033 • There were no significant differences between <i>Tramacet</i> and co-codamol.
				<p>Secondary:</p> <ul style="list-style-type: none"> • Average daily pain intensity scores 	<ul style="list-style-type: none"> • <i>Tramacet</i> was significantly better than placebo (p=0.038); no data given for co-codamol
				<ul style="list-style-type: none"> • Average daily pain relief scores 	<ul style="list-style-type: none"> • <i>Tramacet</i> was significantly better than placebo 1.7 vs. 1.2, respectively, p=0.013; co-codamol was not significantly different from placebo 1.5 vs. 1.2. <i>Tramacet</i> was not statistically superior to co-codamol p=0.072
				<ul style="list-style-type: none"> • Overall rating on medication by patients and investigators 	<ul style="list-style-type: none"> • 68.8% of patients rated <i>Tramacet</i> as good or very good vs. 61.5% of those taking co-codamol and 46.4% taking placebo (p=0.001 for <i>Tramacet</i> vs. placebo). Physicians noted significantly better overall assessments for both <i>Tramacet</i> and co-codamol vs. placebo (p=0.005 and p=0.035, respectively)
6	<p>RCT, USA, multicentre, double-blind, double-dummy – 4 week duration</p> <p>No power statement included in published paper.</p>	<p>462 patients with chronic non-malignant back pain, OA pain or both, enrolled from 58 centres.</p> <p>Patients were eligible if they had:</p> <ul style="list-style-type: none"> • Mild to moderate non-malignant chronic (≥ 6 months) low-back pain or OA of any joint • ≥ 18 years and in good health <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • history of seizure • alcohol or drug abuse within previous year • suicidal tendencies 	<p>Patients discontinued all analgesics 6 hours prior to study. 2:1 randomisation to:</p> <ul style="list-style-type: none"> • <i>Tramacet</i> one or two tablets, 4-6 hourly (max 10/24 hours), plus matched placebo • Co-codamol (30mg/300mg) 	<ul style="list-style-type: none"> • Pain relief 	<p>Day 1, both groups reported pain relief within 30min, which increased until 2 hr and lasted at least 6 hrs</p>
				<ul style="list-style-type: none"> • Total pain relief scores (sum of 6 hourly pain score (PAR) measured on a 5 point Likert scale – to a total maximum of 24 points) 	<p>Mean total pain relief scores were comparable at each visit in both groups (11.9 vs. 11.6 at day 22, respectively, for <i>Tramacet</i> vs. co-codamol)</p>
				<ul style="list-style-type: none"> • Change in pain intensity 	<p>Sum of pain intensity differences (SPID) was similar in both groups at each visit, as was weekly sum of pain intensity difference, maximum pain relief (2.5 vs. 2.4 on a 5-pt scale, 0-4), and overall efficacy (1-5) 2.9 vs. 2.8 on day 22</p>
				<ul style="list-style-type: none"> • Patient global assessment of efficacy 	<p>At end of study, 32% of patients on <i>Tramacet</i> vs. 29% on co-codamol rated treatment very good or excellent</p>

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		<ul style="list-style-type: none"> on MAOIs/tricyclic antidepressants/neuroleptic or any drug that could lower seizure threshold 	<p>one or two capsules, 4-6 hourly (max 10/24 hours), plus matched placebo</p> <ul style="list-style-type: none"> Rescue medication = ibuprofen 400mg when required. 	<ul style="list-style-type: none"> Investigator global assessment of efficacy 	<p>32% of investigators rated <i>Tramacet</i> as very good or excellent compared to 30% for co-codamol (30mg/300mg)</p> <ul style="list-style-type: none"> Mean daily dose was 3.5 tabs/caps in both groups Use of rescue medication was also similar in both groups 80% and 79% of patients in the <i>Tramacet</i> and co-codamol (30mg/300mg) groups completed the study – similar discontinuation rates
Placebo-controlled					
8	<p>RCT – multicentre, USA, double-blind and placebo controlled. 91 day duration</p> <p>Power statement included in published paper.</p>	<p>307 patients randomised, 306 in intention to treat analysis. Patients (40-75 years, mean 61 years) had symptomatic OA of knee or hip for ≥ 1 year with moderate OA pain ($\geq 50/100$mm on visual analogue scale [VAS]) despite treatment with a stable dose of a COX-2 (celecoxib ≥ 200mg/day or rofecoxib ≥ 25mg/day) for at least 2 weeks preceding enrolment</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> use of antidepressants or antiepileptics for pain, sedatives, short-acting analgesics steroid injections in the two months before study history of ankylosing spondylitis, rheumatoid arthritis, active gout or pseudogout previous failure with tramadol or discontinuation due to adverse effects use of tramadol within 30 days of study 	<ul style="list-style-type: none"> <i>Tramacet</i> titrated to one tablet four times a day by day 10 then max 8/24 hours thereafter Placebo 	<p>Primary:</p> <ul style="list-style-type: none"> VAS score <p>Secondary:</p> <ul style="list-style-type: none"> Pain relief rating scores (4=complete, -1= worse) 	<ul style="list-style-type: none"> <i>Tramacet</i> was associated with a lower mean VAS score than placebo (41.5 vs. 48.3, $p=0.025$). 59.5% and 47.7% of patients, respectively, had a $\geq 30\%$ reduction in VAS ($p=0.029$) Final pain relief rating scores were significantly higher for <i>Tramacet</i> than placebo 2.0 vs. 1.6 ($p=0.002$) 67.8% of patients and 71.1% of investigators rated <i>Tramacet</i> as good or very good vs. 54.3% and 54.0% for placebo ($p=0.005$ for patients and $p=0.001$ for investigators) Cumulative time to discontinuation was significantly earlier for placebo than <i>Tramacet</i> ($p=0.016$) 17.0% of patients discontinued treatment with placebo vs. 8.5% with <i>Tramacet</i> ($p=0.029$) <i>Tramacet</i> was statistically superior to placebo for physical function component only ($p=0.049$) <i>Tramacet</i> was only statistically superior for the physical functioning ($p=0.010$) component.
				<ul style="list-style-type: none"> Overall medical assessment at final visit by patients and physicians Cumulative time to discontinuation due to lack of efficacy Patients discontinuing due to lack of efficacy WOMAC OA scores (multidimensional measure of pain, stiffness and physical function) Quality of life, short-form 36 (SF-36) 	

Key:

RCT – randomised controlled trial