Research Review
PRODUCT REVIEW

Nuromol® (Ibuprofen/Paracetamol) for the Acute Relief of Pain and/or Inflammation and Reduction of Fever

About the Reviewer

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John has a broad background in clinical and academic work. Five years ago he became the Clinical Director of Pharmacy Services, which includes a governance role for medication management, throughout Waikato DHB. He is also Clinical Lead for the Health Quality & Safety Commission's Medication Safety programme.

His current working role is a mixture of clinical anaesthesia, medical administration and academic anaesthesia. John is involved with teaching anaesthetic registrars, trainee interns, and 4th year medical students (during their rotation through anaesthesia), and he also contributes to the research output of the Anaesthesia department at Waikato Hospital.

Abbreviations used in this review
AE = adverse event
CI = confidence interval
COX = cyclo-oxygenase
CYP = cytochrome P450
FDC = fixed-dose combination
NNT = number of patients needed to be treated
NSAID = nonsteroidal anti-inflammatory drug
SPRID8 or 12 = sum of pain relief and pain intensity differences over 8 or 12 hours

This review is a summary of clinical data for ibuprofen/paracetamol 200/500 mg fixed-dose combination (FDC) tablets (*Nuromol*®), derived largely from the dental model of acute pain. This is a standard clinical-trial model for analgesic assessment, and from which data are routinely extrapolated to a broad range of other acute pain settings and indications, such as the provision of temporary relief of pain and/or inflammation associated with back pain, period pain, cold and 'flu symptoms, muscular pain, sore throat, rheumatic pain and non-serious arthritic pain, headache, migraine headache, or tension headache in individuals aged 12 years or over. FDC ibuprofen/paracetamol is particularly suitable for pain management when stronger analgesia is required than that provided by either ibuprofen or paracetamol alone.[1-2]

In clinical trials, FDC ibuprofen/paracetamol demonstrated significantly greater efficacy, and with a significantly faster onset of action, and significantly greater patient satisfaction regarding extent of pain relief, than either ibuprofen or paracetamol alone.[1-2] FDC ibuprofen/paracetamol also demonstrated significantly greater analgesic efficacy than paracetamol/codeine or ibuprofen/codeine combination therapy,[3] and also longer-lasting analgesic activity than paracetamol alone and paracetamol/codeine in dental pain studies.[2-4] Regarding adverse events (AEs), a large overview including approximately 35,000 patients revealed that the incidence of AEs for ibuprofen-paracetamol combinations was significantly less than that for placebo.[5]

In summary, extrapolation of data from the standard, acute dental pain model highlights that FDC ibuprofen/paracetamol (*Nuromol*®) has wide-ranging and favourable clinical efficacy and tolerability profiles in numerous acute pain settings. Potential added benefits of FDC therapy include greater patient convenience, synergistic clinical activity, enhanced patient satisfaction with the extent and duration of analgesia, and improved adherence to treatment.

Introduction

Rationale for FDC relief of pain, inflammation and fever

Dual combination analgesic products often provide greater analgesic efficacy than monotherapy with an equivalent dosage of either active constituent. This is the case for FDC ibuprofen/paracetamol tablets.[1,3,6-11]

A key rationale for the use of FDC products is that different sites and modes of action can be provided,[6] with the potential for synergistic analgesic and antipyretic activity.[2] Ibuprofen, for example, is a nonsteroidal anti-inflammatory drug (NSAID) that restricts the synthesis of prostaglandins, and other nociceptive and inflammatory mediators in injured tissues, by inhibiting cyclo-oxygenase (COX) enzymes 1 and 2. The precise mechanism of paracetamol action is not definitively understood. However, experimental evidence suggests that the following factors may be involved: central antinociceptive activity; inhibition of central COX-2 activity; stimulation of descending serotonin pathways, and inhibition of nociceptive signal transmission, in the spinal cord; and weak inhibition of peripheral COX-1 and COX-2 enzymes.[2,6]

Other potentially important advantages for FDCs include improved patient convenience and adherence to treatment, since one rather than two preparations are being used. Moreover, the possibility of synergistic clinical efficacy suggests that, in a FDC, lower doses of the active ingredients can be used (relative to monotherapy); this creates the prospect of improved tolerability.[6,8,9] A longer-lasting clinical effect is also likely to manifest when a FDC of two active ingredients, rather than a single-constituent tablet, is used. Indeed, dental pain studies have shown ibuprofen/paracetamol to have longer-lasting analgesic activity than paracetamol alone or dual therapy with paracetamol plus codeine.[2,3]

Avoidance of codeine-containing preparations

Nonopioid FDCs such as ibuprofen/paracetamol have the added clinical advantage of being codeine-free, which is associated with distinct efficacy and tolerability benefits. Indeed, in the model of acute postoperative dental pain, FDC ibuprofen/paracetamol was significantly more effective than paracetamol/codeine or ibuprofen/codeine combinations.[3] The potential for poor response to codeine-containing

preparations should not be overlooked. That is, codeine requires conversion to morphine by cytochrome P450 (CYP) 2D6, and because of genetic variation in *CYP2D6*, more than 10–20% of individuals are poor metabolisers of codeine and achieve inadequate pain relief when codeine-containing preparations are used.[12] Furthermore, among the up to 90% of individuals who are extensive metabolisers of codeine, the risk of opioid-related AEs and drug interactions may be markedly increased.[12] As outlined in the *Tolerability* section of this review, a large overview of data for up to 35,000 patients revealed that opioids and opioid-containing FDCs were associated with a significantly greater AE incidence than placebo, whereas the converse was true for ibuprofen-paracetamol combinations.[5] Another particularly important issue to consider with over-the-counter or prescription use of codeine-containing preparations is the apparently increased potential for misuse or abuse of such preparations.[13]

Indications for ibuprofen/paracetamol therapy

At various stages in their lives, almost all people experience acute pain, which typically refers to pain of short duration (<12 weeks) that generally has a rapid onset.[9] It often results from tissue or nerve damage, or both, due to accidental injury (e.g. falls, sprains, strains) or surgery.[8,9] Acute pain is often a feature of inflammation, and occasionally swelling, especially in joints and muscles. It may also result from transient dysfunction of a specific body system (e.g. constipation, period pain), or from some type of headache.[9]

The standard industry model for assessing analgesic efficacy against 'everyday pain' is to utilise randomised, double-blind clinical trials of postoperative dental pain after third molar removal.[9] There is then validity in extrapolating analgesic efficacy from this model to other acute pain settings. In such clinical trials, pain is assessed before the analgesic intervention using standard pain intensity scales. Subsequently, pain is evaluated, typically for 6 hours after the intervention, using standard pain intensity and pain relief scales. The standard outcome regarded as an indicator of treatment success is if a patient attains ≥50% of the maximum possible pain relief.[9]

Besides reduction of fever, ibuprofen/paracetamol is indicated for the temporary alleviation of acute pain and/or inflammation, including musculoskeletal pain (back or muscular pain; rheumatic or non-serious arthritic pain), period pain, cold and 'flu symptoms, sore throat, dental pain, and headache (including migraine and tension headache). The FDC should not be used for more than 3 days consecutively without specific advice from a doctor.[2]

Focus on ibuprofen/paracetamol FDC therapy

Pharmacodynamic properties

As mentioned earlier, ibuprofen and paracetamol have different sites and mechanisms of action that lead to synergistic antinociceptive and antipyretic activity. Ibuprofen inhibits prostaglandin synthesis via peripheral inhibition of COX-2 isozymes. This leads to reduced sensitisation of nociceptive afferent nerve terminals to mediators such as bradykinin. In addition, ibuprofen restricts migration of activated leucocytes into inflamed regions; it also has marked antinociceptive activity in the spinal cord, in part because of COX inhibition. Central prostaglandin inhibition in the hypothalamus accounts for the antipyretic activity of ibuprofen, which has also been shown to reversibly restrict platelet aggregation. Overall, ibuprofen limits inflammatory pain, swellings and fever.[2]

The precise mechanism of paracetamol action is poorly understood, although marked evidence exists of a central antinociceptive effect. Biochemical studies suggest that paracetamol is a central inhibitor of COX-2. As already outlined, paracetamol may also enhance activity in descending serotonergic pathways, thereby inhibiting pain signal transmission in the spinal cord. Paracetamol is a very weak inhibitor of peripheral COX-1 and COX-2 isozymes.[2]

Importantly, FDC ibuprofen/paracetamol is particularly appropriate for clinical use when stronger analgesia is needed than that provided by ibuprofen 400 mg or paracetamol 1,000 mg alone, or when faster analgesia is needed than that provided by ibuprofen. Indeed, in a randomised, double-blind study in the model of acute postoperative dental pain after third molar removal:[1]

- FDC ibuprofen/paracetamol had significantly greater ($p<0.0001$) analgesic efficacy than paracetamol 1,000 mg.[1]
- The duration of analgesia provided by FDC ibuprofen/paracetamol was almost twice that provided by paracetamol 500 mg (8.4 vs 4.7 hours), and more than 1½ times that provided by paracetamol 1,000 mg (8.4 vs 5.2 hours; $p<0.001$; **Figure 1**).
- Patient satisfaction with FDC ibuprofen/paracetamol, regarding the provision of 'excellent', 'very good' or 'good' pain relief, was high (88% of patients) and better than that with ibuprofen 200 mg (74%), paracetamol 500 mg (49%), or paracetamol 1,000 mg (66%).

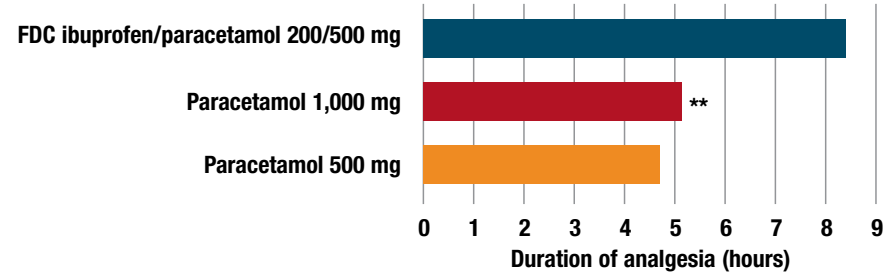

Figure 1. Significantly greater duration of analgesia for FDC ibuprofen/paracetamol 200/500 mg than paracetamol alone in a dental pain model.[1] **p<0.001 vs FDC ibuprofen/paracetamol.

A single-dose, randomised, double-blind, placebo-controlled, dose-ranging trial initially assessed the efficacy and tolerability of various FDCs of ibuprofen/paracetamol (100/250 mg, 200/500 mg, or 400/1000 mg) in 735 adults aged ≥16 years with moderate-to-severe postoperative dental pain.[1] Regarding a primary efficacy endpoint — the sum of pain relief and pain intensity differences over 8 hours (SPRID8) — the 200/500 mg and 400/1,000 mg FDCs of ibuprofen/paracetamol (i.e. dosage equivalent to 1 or 2 *Nuromol*® tablets, respectively) were significantly more effective than the corresponding doses of ibuprofen or paracetamol monotherapies. The use of rescue medication was required by approximately 70–75% of patients who received paracetamol or placebo, compared with 28.0% of patients in the FDC 200/500 mg group and 21.5% of patients in the FDC 400/1,000 mg group. After the initial 8-hour study period, all three FDCs administered *prn* were significantly more effective than placebo ($p<0.001$) over the subsequent 72 hours. For the 200/500 mg FDC, the incidence of treatment-related AEs was significantly less than that for the constituent monotherapies (6.3% vs 16.0% [$p<0.05$] vs 22.4% [$p<0.001$]). Overall, the 200/500 mg and 400/1,000 mg FDCs (i.e. equivalent to 1 or 2 *Nuromol*® tablets) *'… were significantly more effective … than … comparable doses of ibuprofen or paracetamol alone in moderate to severe acute dental pain.'*[1]

In other studies, a single-dose of FDC ibuprofen/paracetamol was shown to provide significantly more effective analgesia than paracetamol/codeine 1,000/30 mg ($p=0.0001$); it was also noninferior to ibuprofen/codeine 400/25.6 mg. A two-tablet dose of FDC ibuprofen/paracetamol also demonstrated a significantly faster onset of action ('confirmed perceptible' or 'meaningful' pain relief) than one or two tablet doses of ibuprofen or paracetamol alone (**Figure 2**).[1]

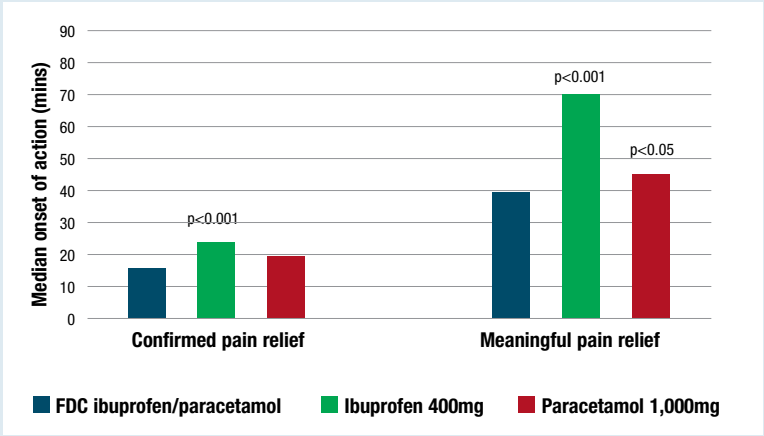

Figure 2. Median times to onset of analgesia produced by FDC ibuprofen/paracetamol versus the individual ingredients.[1] All p values shown are versus the FDC ibuprofen/paracetamol tablet.

Pharmacokinetic properties

The FDC ibuprofen/paracetamol tablet has been formulated to ensure that the active ingredients are simultaneously released and absorbed so that they deliver appropriate combined analgesia;[6] this is important because, from the monoconstituent preparations, ibuprofen dissolves faster in basic conditions than paracetamol, but dissolves slower than paracetamol in acidic conditions. *In vitro* studies have shown that complete dissolution of the FDC ibuprofen/paracetamol tablet occurs 2–3 times faster than that of standard ibuprofen or paracetamol tablets (9 vs 30 vs 20 minutes; **Figure 3**).[4]

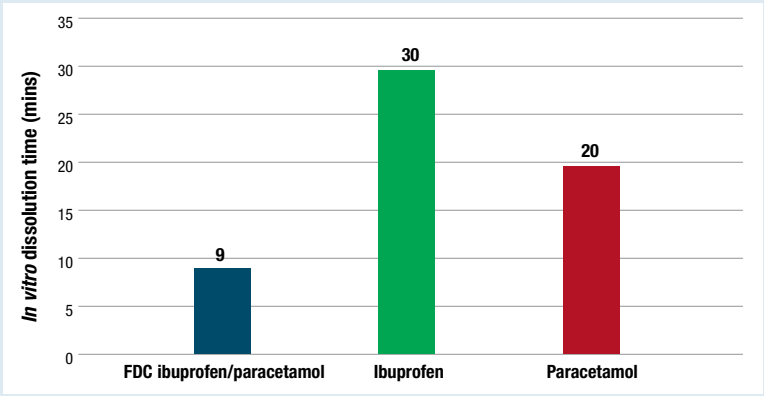

Figure 3. Faster *in vitro* dissolution of FDC ibuprofen/paracetamol than an ibuprofen or paracetamol tablet.[4]

In pharmacokinetic studies in healthy volunteers, the absorption (i.e. rate and extent) of ibuprofen and paracetamol from the FDC formulation was bioequivalent to that from the two monotherapy products.[6] Nevertheless, the rate of paracetamol absorption from the FDC was significantly greater than that from the paracetamol monotherapy tablet: respective median times to peak plasma concentrations were 30 vs 40 minutes ($p<0.05$). Mean plasma concentrations of ibuprofen and paracetamol were markedly greater at earlier timepoints after FDC versus monotherapy administration: for example, at 10 minutes postdose, mean ibuprofen plasma levels were 6.64 versus 0.58 mg/L; corresponding paracetamol levels were 5.43 versus 0.33 mg/L. Thus, except for a potentially earlier onset of analgesia due to enhanced absorption, the FDC of ibuprofen/paracetamol did not markedly alter the pharmacokinetic properties of either ibuprofen or paracetamol monotherapy.[6]

Ibuprofen undergoes hepatic metabolism to two principal metabolites. These are excreted, primarily via the kidneys, either unchanged or as conjugates; a minimal amount of unchanged ibuprofen is also excreted. The elimination half-life of ibuprofen is approximately 2 hours. No major differences in the pharmacokinetic profile of ibuprofen exist between elderly and younger individuals.[2]

Paracetamol is readily absorbed from the gastrointestinal tract. It undergoes hepatic metabolism, and is excreted primarily via the kidneys as sulphate and glucuronide conjugates; approximately 10% of the excretion products comprise glutathione conjugates, and <5% is unchanged paracetamol. The elimination half-life of paracetamol is approximately 3 hours.[2]

Therapeutic efficacy

The specific clinical efficacy of FDC ibuprofen/paracetamol 200/500 mg (*Nuromol*®) has been confirmed in large, randomised, double-blind, placebo-controlled studies in the model of acute postoperative dental pain.[1] In these trials, ibuprofen/paracetamol was significantly more effective than corresponding doses of ibuprofen and paracetamol monotherapies.[1] Another trial in the same model in 678 patients revealed that two tablets of ibuprofen/paracetamol 200/500 mg, regarding the primary study outcome of SPRID12, was significantly more effective than placebo ($p<0.0001$) and two tablets of paracetamol/codeine 500/15 mg ($p\leq0.0001$); analgesia was also significantly greater with two tablets of ibuprofen/paracetamol 200/500 mg than two tablets of ibuprofen/codeine 200/12.8 mg ($p=0.0001$; **Figure 4**).[3]

In addition, one tablet of ibuprofen/paracetamol 200/500 mg was significantly more effective than two tablets of paracetamol/codeine 500/15 mg ($p=0.0001$), and statistically noninferior to two tablets of ibuprofen/codeine 200/12.8 mg. The duration of effect was indicated by median time to the first use of rescue medication, which was numerically greater in the 2-tablet ibuprofen/paracetamol group (597 minutes) than in the other four study groups:

1 tablet of ibuprofen/paracetamol, 491 minutes;

2 tablets of ibuprofen/codeine, 483 minutes;

2 tablets of paracetamol/codeine, 347 minutes;

and placebo, 101 minutes.

Significantly fewer patients in the 2-tablet ibuprofen/paracetamol group than in the other four study groups used rescue medication ($p<0.04$). *'In conclusion, 1 or 2 tablets of … ibuprofen 200 mg/paracetamol 500 mg provided highly effective analgesia that was comparable with, or superior to, other combination analgesics marketed for strong pain. Paracetamol combined with ibuprofen … is a more effective analgesic than codeine combined with ibuprofen …'* and provides *'… a useful alternative analgesic option for people not wishing to take codeine.'*[3]

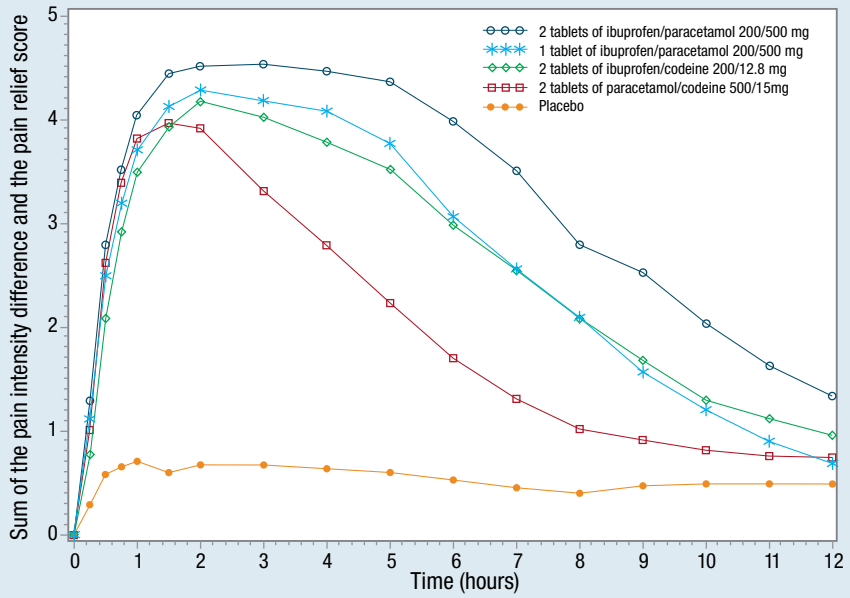

Figure 4. Superior SPRID scores over 12 hours associated with two tablets of ibuprofen/paracetamol 200/500 mg (adapted from Daniels et al.[3]).

A Cochrane overview of the three abovementioned trials pooled data for 1,647 study participants.[8] The proportions of patients attaining ≥50% maximum pain relief over 6 hours were 69% for 1 *Nuromol*® tablet, 72% for 2 *Nuromol*® tablets, 52% for ibuprofen 400 mg alone, and 7% for placebo (**Table 1**). Corresponding proportions of patients requiring rescue medication were 34%, 25%, 48%, and 79%.

Median times to rescue medication use were 7.6 hours for 1 *Nuromol*® tablet, 8.3 hours for 2 *Nuromol*® tablets, and 1.7 hours for placebo. Corresponding proportions of patients experiencing ≥1 AE were 30%, 29%, and 48%. Thus, *'Ibuprofen plus paracetamol combinations provided better analgesia than either drug alone (at the same dose), with a smaller chance of needing additional analgesia over about eight hours, and with a smaller chance of experiencing an adverse event.'*[8]

Two other Cochrane reviews have also recently focused on the efficacy of FDC ibuprofen/paracetamol from the specific viewpoints of non-prescription oral analgesic use for acute pain,[9] and an update of single-dose oral analgesic use for acute postoperative pain in adults.[14] The larger of the two reviews[14] provides an overview of 39 individual Cochrane reviews that included approximately 50,000 participants and almost 500 studies. The overview endorses data outlined in the earlier, pivotal review conducted by Derry et al.[8] Notably, after removal of any publication bias and considering only results deemed reliable, FDC ibuprofen/paracetamol was one of only four products, from a broad range of analgesics, that had an NNT value (1.5–1.6) less than 2. In this context, NNT refers to the number of patients who need to be treated to achieve an additional beneficial outcome of ≥50% maximum pain relief over 4–6 hours relative to placebo; thus, lower NNT values indicate better analgesic efficacy. By way of comparison, other documented NNT values were: aspirin 2.4–4.2; codeine 12; diclofenac 1.9–2.4; ibuprofen + codeine 2.2; naproxen 2.7; paracetamol 3.5–4.6; and paracetamol + codeine 2.2–3.9. The authors concluded that: *'… fixed dose combinations of analgesics can produce good and often long-lasting analgesia at relatively low doses … This should inform choices by professionals and consumers.'*[14]

Table 1. Key clinical outcomes from a large overview of FDC ibuprofen/paracetamol efficacy in acute postoperative pain[8]

Study outcome	FDC ibuprofen/paracetamol 200/500 mg	FDC ibuprofen/paracetamol 400/1,000 mg	Ibuprofen 400 mg alone	Placebo
% pts with ≥50% maximum pain relief over 6 hours	69	73	52	7
NNT (95% CI)	1.6 (1.5, 1.8)[a]	1.5 (1.4, 1.7)[a]	5.4 (3.5, 12)[b]	–
Risk ratio (95% CI)	10.29 (5.70, 18.58)[a]	11.21 (6.18, 20.35)[a]	1.30 (1.10, 1.55)[b]	–
Median time to rescue medication use (hours)	7.6	8.3	–	1.7
% pts using rescue medication within 8 hours	34	25	48	79
NNT (95% CI)	2.2 (1.8, 2.9)[a]	1.8 (1.6, 2.2)[a]	4.3 (3.0, 7.7)[b]	–
Risk ratio (95% CI)	0.46 (0.37, 0.58)[a]	0.31 (0.24, 0.40)[a]	0.57 (0.42, 0.77)[b]	–
% pts with any AE	30	29	55	48
NNT (95% CI)	5.4 (3.6, 10.5)[a]	5.1 (3.5, 9.5)[a]	5.7 (3.6, 14.0)[b]	–
Risk ratio (95% CI)	0.69 (0.55, 0.85)[a]	0.62 (0.50, 0.77)[a]	0.81 (0.66, 0.99)[b]	–

[a] Relative to placebo.
[b] For ibuprofen/paracetamol 400/1,000 mg versus ibuprofen 400 mg alone.
AE, adverse event; CI, confidence interval; FDC, fixed-dose combination; NNT, number needed to treat; pts, patients.

Dosage and administration

The standard ibuprofen/paracetamol 200/500 mg dosage is 1–2 tablets up to 3 times per day; leave ≥6 hours between doses. No more than 6 tablets should be taken in a 24-hour period, and the product should not be used for >3 days without consulting a doctor. The product should not be used by individuals aged <12 years.

Contraindications and precautions

FDC ibuprofen/paracetamol should not be used in patients with: [2]

- Hypersensitivity to ibuprofen, paracetamol or tablet excipients.
- A history of hypersensitivity to aspirin or other NSAIDs.
- A history of gastrointestinal ulceration, perforation or bleeding associated with NSAIDs.
- Coagulation defects.
- Severe hepatic, renal or heart failure, because of a risk of precipitate renal failure.
- Concurrent use of other paracetamol-containing products, NSAIDs, or aspirin >75 mg/day.
- Pregnancy — ibuprofen/paracetamol should not be used during the third trimester because of a risk of premature closure of the foetal ductus arteriosus and possible pulmonary hypertension.

In addition, FDC ibuprofen/paracetamol should be used with caution in the following settings: [2]

- Elderly patients, because of an increased risk of gastrointestinal bleeding and perforation.
- Patients with respiratory disorders (e.g. asthma), because of the potential for precipitate bronchospasm.
- Patients with cardiovascular or cerebrovascular disorders, because of potential fluid retention, oedema, and arterial thrombotic events.
- Patients with systemic lupus erythematosus and mixed connective tissue disorders, because of possible aseptic meningitis.
- Women attempting to conceive, because of potentially impaired female fertility.

Drug interactions

Drug interactions of potential clinical significance between FDC ibuprofen/paracetamol and other products are listed in **Table 2**.[2]

Table 2. Potential clinically significant drug interactions between FDC ibuprofen/paracetamol and other products[2]

Drug	Possible clinical consequences of interaction
Antihypertensives	↓ antihypertensive efficacy
Antiplatelet agents	↑ risk of GI bleeding
Cardiac glycosides (e.g. digoxin)	Worsening heart failure, ↓ GFR, ↑ plasma digoxin levels
Chloramphenicol	↑ plasma chloramphenicol concentration
Cholestyramine	↓ rate of paracetamol absorption
Corticosteroids (e.g. prednisone)	↑ risk of GI bleeding
Cyclosporin	↑ risk of nephrotoxicity
Diuretics	↓ diuretic effect; ↑ risk of nephrotoxicity
Domperidone, metoclopramide	↑ paracetamol absorption
Lithium	↓ elimination of lithium
Methotrexate	↓ elimination of methotrexate
Mifepristone	↓ effect of mifepristone
Quinolones	↑ risk of convulsions
SSRIs	↑ risk of GI bleeding
Tacrolimus	↑ risk of nephrotoxicity
Warfarin, anticoagulants	↑ anticoagulant effect
Zidovudine	↑ risk of haematological toxicity

↑, increase; ↓, decrease; FDC, fixed-dose combination; GFR, glomerular filtration rate; GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor.

Tolerability

Clinical trials with FDC ibuprofen/paracetamol revealed no AEs other than those previously identified for ibuprofen and paracetamol monotherapies. In pharmacovigilance studies, AEs occurring with a common incidence (≥1/100 to ≤1/10 patients) comprised abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting; and abnormal laboratory parameters (e.g. increased alanine aminotransferase and γ-glutamyltransferase, abnormal liver function tests, increased blood levels of creatinine and urea).[2]

A large overview of AEs associated with single-dose oral analgesics, used for the treatment of acute pain in adults, involved approximately 350 studies and about 35,000 patients. Typically, the incidence of AEs for aspirin 1,000 mg, diflunisal 1,000 mg, opioids, or opioid-containing FDCs, was significantly greater than that for placebo. Conversely, the incidence of AEs for ibuprofen-paracetamol combinations was significantly less than that for placebo. Specific risk ratios (and 95% confidence intervals [CIs]) for the occurrence of AEs were: aspirin 1.6 (95% CI: 1.1, 2.3); diflunisal 1.8 (1.2, 2.6); ibuprofen + caffeine 2.2 (1.03, 4.90); dihydrocodeine 3.4 (1.2, 9.8); and paracetamol + codeine 1.4 (1.2, 1.6). The risk ratio for ibuprofen/paracetamol (*Nuromol*®) was only 0.7 (0.6, 0.9). Expressed differently, the number of patients needed to be treated (NNT; relative to placebo) for an additional harmful outcome to manifest was 7.5 (95% CI: 4.8, 17) for aspirin and 7.7 (4.8, 20) for diflunisal; conversely, the NNT to prevent an AE was 5.4 (95% CI: 3.6, 11) for *Nuromol*®.[5]

Take home messages

FDC analgesic therapy has several potential clinical advantages:
  - Synergistic pain relief.
  - Longer-lasting activity.
  - Enhanced patient convenience, satisfaction and adherence to treatment.
  - Improved tolerability.
- FDC ibuprofen/paracetamol (*Nuromol*®) is significantly more effective, and with a significantly faster onset of action and significantly greater patient satisfaction, than either ibuprofen or paracetamol alone.
- FDC ibuprofen/paracetamol (*Nuromol*®) is significantly more effective than paracetamol/codeine or ibuprofen/codeine, and has longer-lasting analgesic activity than paracetamol alone or paracetamol/codeine.
- FDC ibuprofen/paracetamol (*Nuromol*®) has wide-ranging and favourable clinical efficacy and tolerability profiles in various acute pain settings.
- In single-dose studies involving a total of almost 35,000 patients, aspirin, diflunisal, opioids, and opioid-containing FDCs, were associated with a significantly greater incidence of AEs than placebo. The converse was true for ibuprofen-paracetamol combinations.

Availability of FDC ibuprofen/paracetamol in NZ

In New Zealand, FDC ibuprofen/paracetamol 200/500 mg (*Nuromol*®) is available on the General Sales List in pack sizes of 2–20 tablets.
In pack sizes of 24–100 tablets, FDC ibuprofen/paracetamol 200/500 mg (*Nuromol*®) is a Pharmacy Only medicine.

EXPERT'S SUMMARY COMMENT

Some questions are well answered by the available literature. In the wisdom-tooth extraction pain model, the combination of paracetamol and ibuprofen works well, better than either of the active substances alone. The chosen doses, paracetamol 500 mg and ibuprofen 200 mg, per tablet are sensible. These doses match over-the-counter formulations of the two medications when they are supplied as single-agent tablets. The recommended maximum dose frequency for each of the active substances alone, up to four times a day, is the same. For an adult with no specific analgesic precautions, a single tablet is likely to offer reasonable analgesia for pain at the milder end of moderate, and two tablets would be a safe dose for stronger pain.

One of the systematic reviews referenced in this review represents more than 50,000 patients, an impressively large number for pain research; however, the breadth of pain research models examining the evidence base is narrow, and is largely restricted to a single pain stimulus and to single doses of the active substances combined, compared to the individual agents alone or to placebo.

We also lack answers to some important questions. While the current recommendations are for consumers to seek medical advice if they intend to use the product for more than 3 days, it would be useful to understand the product's side-effect profile in longer-term use. The data about AEs in this review clearly show that the placebo group had more side effects, which seems unlikely in a real-world setting. There are other more subtle concerns. For example, what is the risk that a person who is intolerant to NSAIDs takes *Nuromol*® without realising that the tablet contains ibuprofen or the converse when considering paracetamol? In a similar vein what is the risk that a healthcare worker double doses a patient on paracetamol or NSAID because of confusion about which painkiller the patient had recently taken? *Nuromol*® and *Nurofen*® share a common stem, and this style of naming has caused problems with some of the insulin products (*Novorapid*® versus *Novomix*®).

There is no doubt that *Nuromol*® rolls off the tongue easier than saying paracetamol and ibuprofen, so this tradename is likely to be commonly used when verbally requesting or discussing medications. Ultimately, it is the combination of effectiveness, convenience, and clever packaging that will make this medicine popular. The tablet has excellent rapid release characteristics, a sensible combination of doses of two popular simple analgesics, and a name that already sounds familiar. However healthcare workers and consumers will need to be mindful of the potential for confusion in order to avoid unwittingly taking the wrong medicine or doubling up on doses.

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