New Medicine Assessment

Nefopam

Recommendation: Amber 0 for the following indications:

For the relief of persistent pain unresponsive to other non-opioid analgesics.

Prescribers should carefully consider whether the potential benefits outweigh the risks of adverse effects in individual patients. Prescribers should be cautious of the anticholinergic burden of nefopam, particularly in the elderly.

Treatment should be reviewed regularly and stopped if benefits are not seen in the short term.

Summary of supporting evidence:

- Nefopam is totally distinct from other centrally-acting analgesics and therefore provides an additional treatment option in difficult to treat patients
- Evidence for the use of oral nefopam is very limited; most evidence for nefopam relates to short-term use in a post-operative setting, often administered intravenously
- Evidence for use in chronic pain is restricted to several small studies from the 1980s
- NICE does not support the use of nefopam in any guidance
- Nefopam is commonly associated with adverse drug reactions (particularly in the elderly), is toxic in overdose, and has the potential for abuse
- Cost is comparable with weak opiates, but more expensive than NSAIDs
- Pan Mersey support prescribing of nefopam, GMMMG restrict its use

Details of Review

Name of medicine (generic & brand name)**:**

Nefopam

Strength(s) and form(s):[1]

Film-coated tablets 30mg and 60mg

Dose and administration:[1]

Adults: Dosage may range from 1 to 3 tablets three times daily depending on response. The recommended starting dosage is 2 tablets three times daily.

Elderly: Elderly patients may require reduced dosage due to slower metabolism. It is strongly recommended that the starting dose does not exceed one tablet three times daily as the elderly appear more susceptible to; in particular, the CNS side effects of nefopam and some cases of hallucinations and confusion have been reported in this age group.

Paediatric population

The safety and efficacy of nefopam has not been evaluated in children under 12 years, no dosage recommendation can be given for patients under 12 years.

Renal impairment

Patients with end stage renal disease might experience increased serum peak concentrations during treatment with nefopam. In order to avoid that, it is recommended the daily dose should be reduced not

only for the elderly, but also for patients with terminal renal insufficiency.

BNF therapeutic class / mode of action:

Analgesics.

Nefopam is a potent and rapidly-acting analgesic. It is totally distinct from other centrally-acting analgesics such as morphine, codeine, pentazocine and propoxyphene.[1]

The mechanism of action is not well understood. It is known to inhibit the re-uptake of neurotransmitters including serotonin, noradrenaline and dopamine. Additionally, it blocks sodium and calcium channels in the central nervous system.[3]

Licensed indication(s):

Nefopam is indicated for the relief of acute and chronic pain, including post-operative pain, dental pain, musculo-skeletal pain, acute traumatic pain and cancer pain.

Proposed use (if different from, or in addition to, licensed indication above):

Course and cost:

90 x 30mg tablets £3.18

If taken daily, cost £3.18 - £9.54 /month

Drug tariff Dec 2024

Current standard of care/comparator therapies:

Non-opioid analgesics (paracetamol and NSAIDs)

Weak opioid analgesics (codeine, dihydrocodeine)

Strong opioid analgesics (morphine, buprenorphine, fentanyl, oxycodone)

Anti-depressants (fluoxetine, amitriptyline, citalopram)

Relevant NICE guidance:

Low back pain and sciatica in over 16s: assessment and management [NG59]

Pharmacological management of sciatica - No evidence was identified for paracetamol, nefopam or muscle relaxants other than benzodiazepines for the management of sciatica. The committee agreed that none of these are widely prescribed for sciatica. They noted that advice is already included in this guideline for the use of paracetamol for people with low back pain. Therefore, no further recommendations were made regarding management of sciatica alone, and these medicines do not warrant further research.

Rheumatoid arthritis in adults: management [NG100]

Symptom control - There was limited evidence on paracetamol, opioids and tricyclic antidepressants and no evidence for nefopam, gabapentinoids or selective serotonin reuptake inhibitor (SSRI) and SSNRI antidepressants.

Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain [NG193]

Perioperative care in adults [NG180]

Neuropathic pain in adults: pharmacological management in non-specialist settings [CG173]

Background and context

Nefopam is a non-opioid analgesic drug for moderate pain. It may have a place in the relief of persistent pain unresponsive to other non-opioid analgesics. It causes little or no respiratory depression, but sympathomimetic and antimuscarinic side-effects may be troublesome.[2]

There is little guidance locally or nationally on the use of nefopam.

Summary of evidence

Summary of efficacy data in proposed use:

General

Specialist Pharmacy Service (2024)[3]

Nefopam appears no more potent than non-steroidal anti-inflammatory drugs (NSAIDs), but is commonly associated with adverse drug reactions and is toxic in overdose. It may sometimes be preferred when alternatives are contraindicated or ineffective, or used as add-on therapy when pain is inadequately controlled.

Prescribers should carefully consider whether the potential benefits outweigh the risks of adverse effects in individual patients. Treatment should be reviewed regularly and stopped if benefits are not seen in the short term.

Most evidence for nefopam relates to short-term use in a post-operative setting. Evidence for use in this setting is still limited and conflicting. Evidence for use in chronic pain is restricted to several small studies.

- *Additional benefit demonstrated*
  A 1986 study evaluated the effectiveness of nefopam to manage pain in rheumatoid arthritis. Patients included were already taking a maximum dose of an NSAID. Nefopam was more effective than placebo in reducing pain and morning stiffness, although subjective measures were used. Joint tenderness also improved with nefopam.
- *Similar benefit demonstrated*
  A 1989 study comparing nefopam to flurbiprofen in osteoarthritic pain found no significant difference in effectiveness. More side-effects were experienced with nefopam.
  Another 1989 study comparing nefopam to diclofenac and codeine plus aspirin for cancer pain found similar effectiveness between the treatments. More patients on nefopam withdrew from the study due to side-effects, predominantly nausea.
- *No additional benefit demonstrated*
  A 1988 study evaluated the effectiveness of nefopam to manage pain in rheumatoid arthritis. No statistically significant improvement in pain was observed with nefopam when compared with placebo. The study had a high dropout rate with one main reason being adverse effects of nefopam.
- *Lack of evidence*
  No studies comparing nefopam to centrally-acting analgesics such as tricyclic antidepressants or gabapentinoids were identified.

SIGN 136 - Management of chronic pain (2019)[4]

The evidence identified on the use of nefopam for chronic pain relief is not sufficient to support a recommendation.

[NB. An update to this guideline is in development].

National Library of Medicine (2024)[5]

Nefopam is not approved in the United States by the Food and Drug Administration.

Cochrane - Neuromodulators for pain management in rheumatoid arthritis (2012)[6]

The aim of this review was to determine the efficacy and safety of neuromodulators in pain management in patients with RA. Four trials with high risk of bias were included in this review. Two trials evaluated oral nefopam (52 participants).

The pooled analyses identified a significant reduction in pain levels favouring nefopam over placebo

(weighted mean difference (WMD) -21.16, 95% CI -35.61 to -6.71; number needed to treat (NNT) 2, 95% CI 1.4 to 9.5) after two weeks. There were insufficient data to assess withdrawals due to adverse events. Nefopam was associated with significantly more adverse events (RR 4.11, 95% CI 1.58 to 10.69; NNTH 9, 95% CI 2 to 367), which were predominantly nausea and sweating.

There is currently weak evidence that oral nefopam is superior to placebo in reducing pain in patients with RA. However, it is associated with a significant side effect profile and the potential harms seem to outweigh any modest benefit achieved.

RCGP Secure Environments Group: Safer Prescribing in Prisons (2011)[7]

Nefopam is a non-opioid centrally-acting analgesic for moderate pain. The evidence base is limited, however it may have a use where other non-opioid analgesics are ineffective, but sympathomimetic and antimuscarinic side effects may be a problem.

Consider before opiate analgesia in selected individuals where other non-opioid analgesics ineffective.

Post operative analgesia

The OCTOPUS study [NB. Nefopam route IV] (2018)[8]

The objective of this multicentre, randomised, double-blind controlled trial was to compare the morphine-sparing effects of different combinations of three non-opioid analgesics - paracetamol (P), nefopam (N), and ketoprofen (K)- for postoperative analgesia.

Patients from 10 hospitals were randomised to one of eight groups. Treatments were given intravenously four times a day during the first 48 h after surgery, and morphine patient-controlled analgesia was used as rescue analgesia. The outcome measures were morphine consumption, pain scores, and morphine-related side-effects evaluated 24 and 48 h after surgery.

Despite a failure to reach a calculated sample size, 24 h morphine consumption [median (interquartile range)] was significantly reduced in the paracetamol/nefopam/ketoprofen group [5 (1-11) mg] compared with either the control group [27 (11-42) mg; $P<0.05$] or the nefopam group [21 (12-29) mg; $P<0.05$]. Results were similar 48 h after surgery. No difference was observed in the incidence of morphine-related side-effects.

Systematic review: Pain management after laparoscopic cholecystectomy (2024)[9]

Laparoscopic cholecystectomy can be associated with significant postoperative pain that is difficult to treat. A systematic review was performed using the procedure-specific postoperative pain management (PROSPECT) methodology. Nefopam is not recommended due to lack of evidence.

Double-Blind, Placebo-Controlled, Randomized Trial: Total Knee Arthroplasty (2024)[10]

In this prospective, double-blind, placebo-controlled, randomized trial, 100 patients who underwent TKA at were randomized to either the nefopam or the control group. After surgery, patients in the nefopam group received 200 mg of celecoxib, 150 mg of pregabalin, and 40 mg of nefopam twice daily to control postoperative pain. Oxycodone hydrochloride (10 mg) was used as the rescue analgesic. If the pain remained poorly controlled, 10 mg of morphine hydrochloride was injected subcutaneously as a secondary rescue analgesic.

Patients in the nefopam group had significantly lower postoperative oxycodone and morphine consumption within 24 hours after surgery and during hospitalization, lower VAS pain scores at rest and during motion within 24 h after surgery, better functional recovery on postoperative days 1 and 2, and a shorter hospital stay. However, the absolute reduction in 0 to 24 h opioid consumption, VAS pain scores, and knee range of motion did not exceed the reported minimal clinically important difference.

Cochrane - Single dose oral nefopam for postoperative pain in adults (2009)[11]

This review sought to evaluate the efficacy and safety of oral nefopam in acute postoperative pain, using clinical studies of patients with established pain, and with outcomes measured primarily over 6 hours using standard methods. No included studies were identified after examining in detail thirteen studies on oral nefopam in participants with established postoperative pain. In the absence of evidence of efficacy for oral nefopam in acute postoperative pain, its use in this indication is not justified. Because trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies are lacking, use in other indications should be evaluated carefully. Given the large number of available drugs of this and similar classes, there is no urgent research agenda.

Analgesia in older persons

Review article (2024)[12]

Nefopam is a nonopioid centrally acting analgesic, mainly used in post-operative care and in emergency departments. It is not recommended for older patients due to the risk of disorientation and hallucinations. It is contraindicated in patients with a history of seizures, severe renal or hepatic insufficiency, heart rhythm disorders or angina and taking monoamineoxydase inhibitors (MAOI), up to 3 weeks after their withdrawal. Because of its anti-cholinergic activity and potential additive effect with anti-cholinergics and sympathicomimetics, it should be used with caution in patients at risk of or presenting with acute urine retention or angle closure glaucoma.

Recommendations in acute and chronic pain: Nefopam is not recommended in older people.

Analgesia in critically ill patients

Systematic review and meta-analysis (2020)[13]

This systematic review and meta-analysis addresses the efficacy and safety of nonopioid adjunctive analgesics for patients in the ICU.

Use of any adjuvant in addition to an opioid as compared to an opioid alone led to reductions in patient-reported pain scores at 24 hours. Reductions in opioid use were demonstrated with nefopam (mean difference, 70.89mg less; 95% CI, 64.46–77.32mg less; low certainty).

Summary of safety data:

Analysis of the French Pharmacovigilance database (2007)[14]

Nefopam is widely used for the relief of moderate acute pain in France. All cases of adverse drug reactions (ADRs) associated with nefopam, registered in the French Pharmacovigilance database from January 1, 1995 to December 31, 2004, were reviewed. A total of 114 ADRs were analysed. The most frequent ADRs included 'expected' ADRs such as sweating, nausea, tachycardia, malaise or vomiting; 61 ADRs were 'unexpected. No overdose was reported; 26 ADRs (23%) were considered as 'serious'. Most of them were 'unexpected', including neuropsychiatric (hallucinations, convulsions) or cutaneous (pruritus, erythema, urticaria) ADRs. Six cases of anaphylactic ADRs (two angioedema and four anaphylactic shocks) were reported, all occurring shortly after use of nefopam during the post-operative period. Physicians should be aware of the possible occurrence of some serious ADRs when using nefopam such as convulsions and anaphylactic shocks, especially when the drug is used in special medical conditions, like post-operative periods.

Summary of product characteristics[1]

Contra-indications

Hypersensitivity to the active substance or to any of the excipients.

Nefopam is contra-indicated in patients with a history of convulsive disorders and should not be given to patients taking mono-amine-oxidase (MAO) inhibitors.

Special warnings and precautions for use

The side effects of nefopam may be additive to those of other agents with anticholinergic or sympathomimetic activity. It should not be used in the treatment of myocardial infarction since there is no clinical experience in this indication. Hepatic and renal insufficiency may interfere with the metabolism and excretion of nefopam.

Nefopam should be used with caution in patients with angle closure glaucoma. Cases of nefopam dependence and abuse have been reported with nefopam use.

Nefopam should be used with caution in patients with, or at risk of, urinary retention. Rarely a temporary, harmless pink discolouration of the urine has occurred.

Interaction with other medicinal products and other forms of interaction

Caution should be exercised when nefopam is administered concurrently with tricyclic antidepressants.

It should be noted that nefopam may interfere with some screening tests for benzodiazepines and opioids. These tests for benzodiazepines and opioids may give false positive results for patients taking nefopam.

The following undesirable effects have been reported with the following frequency:

Not known (cannot be estimated from the available data)

System organ class	Frequency	Undesirable effects
Immune system disorders	Not known	Allergic reaction, anaphylactic reactions
Psychiatric disorders	Not known	Nervousness, convulsions, confusional state, hallucination, insomnia
Nervous system disorders	Not known	Light-headedness, syncope, dizziness, paraesthesia, tremor, drowsiness, headache, coma
Eye disorders	Not known	Blurred vision
Cardiac disorders	Not known	Palpitations, tachycardia
Vascular disorders	Not known	Hypotension
Gastrointestinal disorders	Not known	Nausea, vomiting, dry mouth, gastrointestinal disturbances (including abdominal pain and diarrhoea)
Skin and subcutaneous tissue disorders	Not known	Angioedema, sweating
Renal and urinary disorders	Not known	Urinary retention

Strengths and limitations of the evidence:

Strengths

- Nefopam is totally distinct from other centrally-acting analgesics and therefore provides an additional treatment option in difficult to treat patients
- There is currently weak evidence that oral nefopam is superior to placebo in reducing pain in patients with RA
- Cost is comparable with weak opiates, but more expensive than NSAIDs
- Pan Mersey support its use, where as GMMMG severely restrict its use

Limitations

- Evidence for the use of oral nefopam is very limited; most evidence for nefopam relates to short-term use in a post-operative setting, often administered intravenously
- Evidence for use in chronic pain is restricted to several small studies from the 1980s
- The elderly are more susceptible to the CNS side effects of nefopam and anticholinergic burden
- NICE does not support the use of nefopam in any of its guidance
- Data from France where nefopam is more widely used suggests that serious ADRs can occur with nefopam use and there is potential for abuse

Summary of evidence on cost effectiveness:

No cost-effectiveness evaluation has been found.

Prescribing and risk management issues:

- Dose adjustment is needed in the elderly and renally impaired
- There is no guidance to support prescribers in its use
- Commonly associated with adverse drug reactions and is toxic in overdose
- Abuse potential
- Side effects may be additive to those of other agents with anticholinergic or sympathomimetic activity

Commissioning considerations:

Innovation, need and equity implications of the intervention:

Pharmacological options for pain relief are limited in some populations (e.g. older persons) due to the side effect profile of opiates and NSAIDs. Nefopam is an alternative to opiates.

Financial implications of the intervention:

90 x 30mg tablets £3.18

If taken daily, cost £3.18 - **£9.54 /month per patient.**

Over a 6 month period 8222 prescriptions for nefopam 30mg were dispensed in L&SC ICB, with a total cost of £34 214 (equivalent to an annual cost of £68 428).

NB. 5897 of these prescriptions were in Blackpool and Fylde&Wyre.

Other analgesics for moderate pain

Ibuprofen 84 x 400mg tablets £2.63

Codeine 100 x 30mg tablets £4.04

Dihydrocodeine 100 x 30mg tablets £7.79

Morphine MR capsules 60 x 10mg £3.47

Service Impact Issues Identified:

None identified

Equality and Inclusion Issues Identified:

None identified

Cross Border Issues Identified:

The **Pan Mersey APC** RAG rate nefopam as Green.

The **Greater Manchester Medicines Management Group** (GMMMG) consider nefopam a Grey* product, RAG rated as Green with the following caveats:

- Only to be used in patients with moderate to severe chronic liver disease who require analgesia stronger than paracetamol and in whom NSAIDS and moderate strength opiates are contraindicated
- Due to the high cost of nefopam, a lack of evidence of superior efficacy over other analgesics, and

its side effect profile, there is no rationale for routine use. * Products which are not suitable for routine prescribing but suitable for exceptional use in a defined patient population. Prescribers should ensure that more suitable alternatives have been considered and ruled out as not being appropriate before recommending or prescribing a medicine with a GREY list status.
Legal Issues Identified:
None identified
Media/ Public Interest:
None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

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[5] National Library of Medicine, “Nefopam”, June 2024

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