CCG Logo

Commissioning Statement

Treatment	Nefopam
For the treatment of	Pain
Commissioning position	.....CCG does not support the use of nefopam except for the following exceptions: • only following a successful trial by the specialist pain service when all other medications are ineffective, have intolerable side effects or are contraindicated. Treatment should be reviewed on a regular basis and stopped when benefits are not seen or unacceptable side effects develop. In primary care, nefopam should not be initiated; and it should only be continued following initiation and a successful trail from a specialist pain service. Nefopam should not be prescribed in primary care for any other indication, including post-operative pain management. This should be supplied in full by the provider. (North Kirklees/Greater Huddersfield/Wakefield/Calderdale/Bradford City Bradford Districts/Airedale, Wharfedale and Craven)
Date effective from	……..2019
Policy to be reviewed by	……..2022 (to be reviewed earlier if NICE issues guidance)
Background information	Nefopam is a centrally-acting but non-opioid analgesic [1]. It is licensed for patients aged 12 and over for the relief of acute and chronic pain [2]. It has been available for the treatment of pain since the mid-1970s [3].
Summary of evidence/ rationale	**Guidelines:** NICE guideline (NG100) on the management of rheumatoid arthritis (RA) in adults states that there was no evidence of benefit from nefopam in RA [4]. SIGN guidance for chronic pain says that the evidence for nefopam is not sufficient to support a recommendation to use [5]. Nefopam has not been reviewed by the Scottish Medicines Consortium or the All Wales Medicines Strategy Group. **Clinical effectiveness:** A Cochrane Review of single doses of oral nefopam did not find any evidence of efficacy in acute postoperative pain. The authors conclude that its use in this indication is not justified. As trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies are lacking, use in other indications should be evaluated carefully [1].

In surgical patients, nefopam was thought to have similar analgesic potency to non-steroidal anti-inflammatory drugs [3].

Safety:

Between 1978 and 2019, 876 spontaneous reports of adverse events had been reported on yellow cards. 22 fatalities have been reported, including ones due to arrhythmias, suicide and overdosage [6].

Nefopam interacts with many frequently-used medicines. The side effects of nefopam may be additive to those of other agents with anticholinergic or sympathomimetic activity. Nefopam can cause serious increases in blood pressure when combined with phenelzine, isocarboxazid and tranylcypromine [7].

Nefopam needs to be used with caution in older patients and patients with urinary retention. Older people appear to be more susceptible to central nervous system side effects. Some cases of confusion and hallucinations have been reported in this age group [2]. Usage of nefopam contributes to the anticholinergic burden. It has an anticholinergic burden (ACB) score of 2. Medicines with scores of 2 or 3 may increase the risk of cognitive impairment by 46% over 6 years. In addition, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death [8].

Adverse effects associated with nefopam include nausea, sweating, tachycardia, blurred vision, confusion, seizures and urinary retention. It has not been associated with respiratory depression [2].

In overdosage nefopam can cause coma, convulsions, hallucinations, agitation, tachycardia with a hyperdynamic circulation [2]. Serotonin syndrome may occur. TOXBASE notes that this agent is potentially very toxic and hospital clinicians managing patients who have taken too much are encouraged to discuss serious cases with the poisons information service. All patients who have been exposed to this product as a result of self-harm should be referred for assessment. Anyone who has ingested 12 mg/kg or more or people who are symptomatic, should be referred for medical assessment. In cases where the volume of tablets is known, a 19 year old male died after ingesting 1.8g of nefopam (with 700mg diclofenac) and 9 people survived following supportive care after taking 600mg to 1.8g of nefopam [9].

Nefopam has abuse potential through its psychostimulant-like effects. A report of 3 people who abused nefopam shows that abuse has been associated with violent behaviour, myoclonus and sweating. The people who had attempted withdrawal following nefopam abuse experienced depressive symptoms [10].

A Cochrane Review on neuromodulators for RA states that with many other safer analgesics available on the market today and no head-to-head trials suggesting superior efficacy, the authors do not support the use of nefopam in patients with RA [11].

No protocols for switching patients from nefopam to alternatives have been identified. Following chronic usage it may be prudent to withdraw treatment slowly and gradually. In a letter to colleagues, Dr Allistair Dodds, Consultant

	in Pain Medicines at Sunderland Royal Hospital says that given its likely action on dopaminergic, serotonergic and noradrenergic pathways, abrupt cessation is not recommended. He suggests slow tapering of the dose with regular review, and vigilance for central nervous system effects. Psychological addiction should be considered if dose reduction triggers dysphoria, agitation or anxiety [12]. **Cost/resource impact:** Nefopam is currently more expensive than analgesics such as co-dydramol 10/500 and tramadol 50mg.
	References: 1. Kakkar M, Derry S, Moore RA, McQuay HJ. Single dose oral nefopam for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD007442. DOI: 10.1002/14651858.CD007442.pub2 2. DataPharm. electronic Medicines Compendium. Nefopam hydrochloride 50mg film-coated tablets. Galen Ltd. Last updated on eMC 9.5.2019. Accessed from https://www.medicines.org.uk/emc/ on 29.5.2019 3. M. S. Evans, C. Lysakowski, M. R. Tramèr. Nefopam for the prevention of postoperative pain: quantitative systematic review. *British Journal of Anaesthesia 2008;*101(5):610–17 4. NICE. Rheumatoid arthritis in adults: management. NICE guideline 100. Published July 2018. Accessed from https://www.nice.org.uk/guidance/ng100 on 29.5.2019 5. SIGN. Management of chronic pain. Published December 2013. Accessed from https://www.sign.ac.uk/sign-136-management-of-chronic-pain.html on 29.5.2019 6. MHRA. Interactive Drug Analysis Profile. Nefopam. Reports processed up to 31.3.2019. Accessed from https://info.mhra.gov.uk/drug-analysis-profiles/dap.html?drug=./UK_EXTERNAL/NONCOMBINED/UK_NON_000210098015.zip&agency=MHRA on 29.5.2019 7. British Medical Association/Royal Pharmaceutical Society. BNF. Nefopam. Accessed from MedicinesComplete https://www.medicinescomplete.com/#/ on 29.5.2019 8. Fox C, Richardson K, Maidment I et al. Anticholinergic medication use and cognitive impairment in the older population: the Medical Research Council Cognitive Function and Ageing Study. Journal of the American Geriatric Society 2011;59(8):1477-83 9. NPIS Edinburgh. Toxbase. Nefopam hydrochloride. Updated September 2017. Accessed from https://www.toxbasebackup.org/poisons-index-a-z/n-products/nefopam-hydrochloride-/ on 29.5.2019 10. Villier C and Mallaret MP. Nefopam Abuse. Case Report. Accessed from https://journals.sagepub.com/doi/10.1345/aph.1C017 on 29.5.2019 11. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD008921. DOI: 10.1002/14651858.CD008921.pub 12. Dr Allistair Dodds. RE: Information following removal of nefopam from formulary. Letter dated 25.1.2016. Accessed from

	https://sunderlandccg.nhs.uk/wp-content/uploads/2016/03/Removal-of-Nefopam-from-formulary-letter.doc on 17.6.2019
Contact for this policy	**Head of Medicines Optimisation**