

Date: 31st January 2005

Reference: CEM/CMO/2005/2

WITHDRAWAL OF CO-PROXAMOL PRODUCTS AND INTERIM UPDATED PRESCRIBING INFORMATION

Dear Colleague,

I am writing to tell you the advice of the Committee on Safety of Medicines (CSM) in the light of its recent review of the risks and benefits of co-proxamol. In summary, the efficacy of co-proxamol is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable. CSM has therefore advised that:

- In relation to safety, there is evidence that fatal toxicity may occur with a small multiple of the normal therapeutic dose and a proportion of fatalities are caused by inadvertent overdose. Pharmacokinetic and pharmacodynamic interactions with alcohol further reduce the threshold for fatal toxicity.
- There is no robust evidence that efficacy of this combination product is superior to full strength paracetamol alone in either acute or chronic use.
- It has not been possible to identify any patient group in whom the risk:benefit may be positive.
- Co-proxamol products should be withdrawn altogether over the next 6-12 months.
- During the withdrawal phase, interim restrictions and warnings regarding the use of co-proxamol should be introduced to the product information.

Background

Co-proxamol contains a dose of paracetamol (325mg) that would on its own be considered sub-therapeutic, and dextropropoxyphene (32.5mg), a weak opioid analgesic that is known to be toxic in overdose. Each year there are 300-400 fatalities following deliberate or accidental drug overdose involving co-proxamol in England and Wales alone. Approximately one-fifth of these deaths are considered to be accidental. Co-proxamol is second only to tricyclic antidepressants as an agent of fatal prescription drug overdose. Combination with alcohol or Central Nervous System depressants is particularly hazardous and a small multiple of the recommended dose may cause fatal apnoea or cardiac arrhythmia.

Previous CSM action

This is not a new safety concern. CSM first warned prescribers about the risks of co-proxamol in 1985 but despite being rated as 'less suitable for prescribing' by the British National Formulary, it is still widely used. In June 2004 the CSM issued a public request for information regarding the risks and benefits of co-proxamol. From the responses received it was not possible to identify any patient group or indication where the objective evidence of efficacy of co-proxamol outweighed the risks of toxicity.

In order to minimise disruption of healthcare provision, co-proxamol will be phased out so that patients currently receiving co-proxamol may be switched to alternative pain management regimes at their next routine medication review. Meanwhile no new patients should start co-proxamol therapy.

Interim prescribing advice pending withdrawal of co-proxamol

The product information for co-proxamol has been amended as follows:

Indications:

- For the treatment of mild to moderate pain in adults where first line analgesics have proved ineffective or are inappropriate. Co-proxamol should not be used for *any* acute pain indication.
- Co-proxamol therapy should not be initiated in new patients.
- Co-proxamol should not be used in patients aged <18 years

Co-proxamol is contraindicated in:

- Patients who are alcohol-dependent or who are likely to consume alcohol whilst taking co-proxamol.
- Patients who are suicidal or addiction-prone.

Special warnings to give your patients:

- *never* exceed the recommended dose.
- *never* consume alcohol while taking a course of co-proxamol
- Dispose of any unused supplies of co-proxamol (through a pharmacist) as soon as possible after completing treatment.

Management of patients currently taking co-proxamol

The CSM has provided advice on pain management options to assist prescribers in choosing alternative pain management strategies. The CSM's overview of alternative analgesic options is attached at Annex 1.

An alternative pain management regimen should be introduced during the course of normal medical care, e.g. at a routine periodic medication review.

Patients should be reassured that although co-proxamol will not be available indefinitely, they do not need to stop taking co-proxamol *immediately* and there is no cause for alarm, provided the medicine is taken in the prescribed way.

Sources of further information

MHRA website at www.mhra.gov.uk

Current Problems in Pharmacovigilance Volume 30 Oct 2004

<http://medicines.mhra.gov.uk/aboutagency/regframework/csm/csmhome.htm>

Professor Gordon Duff
Chairman
Committee on Safety of Medicines

ADVICE ON ANALGESIC OPTIONS IN TREATMENT OF MILD TO MODERATE PAIN IN ADULTS

General Principles

General principles of pain management advised by current guidelines include:

1. Diagnosis Adequate assessment and accurate diagnosis of the cause of acute or chronic pain is essential for specific treatment options to be pursued.
2. Acute on chronic pain Acute pain may arise on a background of chronic pain, for example due to superimposition of osteoporotic vertebral collapse or nerve entrapment upon other pre-existing conditions. Pain management strategy as for an acute episode is advised.
3. Progressive conditions In a proportion of patients the underlying disease will be expected to deteriorate, in both malignant and non-malignant conditions, and the pain management strategy will require continual adjustment.
4. Psychosocial factors may contribute to pain severity, and should be treated and/or referred if necessary.
5. Non-drug interventions should be considered. Topical rubifacients or other therapies, for example, Trans-Epidermal Nerve Stimulation (TENS) may be beneficial to some patients.
6. Pharmacological interventions should be increased to full therapeutic and tolerated doses before switching to a different agent.
7. Patient requirements All treatment strategies need to be individualised to specific patient requirements and tolerance. Particular formulations may meet individual patient needs such as modified release or skin patch presentations.
8. Combination analgesics Individual patient treatment strategies should be worked out on the basis of single constituent analgesics where each component can be titrated independently. Fixed combination analgesics have a limited role in pain management, but may be convenient for patients so as to reduce the overall quantity of tablets. If combination preparations are used, prescribers are encouraged to give therapeutic doses e.g. codeine 30mg and paracetamol 500mg per tablet.
9. Guidelines Additional sources of data on analgesics and published pain management guidelines should be consulted for detailed information. These include the Summary of Product Characteristics and patient information leaflets for specific products, the British National Formulary (BNF), the National Prescribing Centre (NPC), Scottish Intercollegiate Guidelines Network (SIGN), Prodigy NHS, the Pain Society and the World Health Organisation (WHO)¹.

¹ <http://www.bnf.org/> <http://www.npc.co.uk/> <http://www.sign.ac.uk/>
<http://www.prodigy.nhs.uk/> <http://www.painsociety.org/>

Pain Management Strategies for Acute and Chronic Mild to Moderate Pain in Adults

Treatment strategies are considered in the following clinical settings where pharmacological agents can be introduced in a step-wise manner.

- I Acute pain either as a self-limiting episode or on a background of chronic pain
- II Chronic pain due either to stable or progressive conditions.

Class I – Acute pain either as acute self-limiting episode or on a background of chronic pain: e.g. soft tissue injuries, post-operative pain, osteoarthritis, low back pain, dysmenorrhoea.

- Step 1: Paracetamol
- Step 2: Substitute ibuprofen
- Step 3: Add Paracetamol to Ibuprofen
- Step 4: Continue paracetamol and replace ibuprofen with an alternative NSAID

An alternative approach where NSAIDs are contraindicated or not recommended (see product information) is to substitute a low potency opioid e.g. codeine or dihydrocodeine for the NSAID in place of, or in addition to full dose of paracetamol at steps 2 and 3. Where pain is not controlled on Step 4, a low potency opioid e.g. codeine or dihydrocodeine may be added.

Class IIa – Chronic stable pain requiring long-term regular analgesic use e.g. in osteoarthritis

Steps 1 to 4 above may be effective for many patients.

Where chronic pain is not controlled after Step 4, the addition of a low potency opioid at therapeutic doses should be considered early in the management of chronic pain:

Step 5: Full therapeutic dose of low potency opioid e.g. codeine or dihydrocodeine in addition to full dose of NSAID or paracetamol.

Most patients will respond to this regimen, but for the small minority who do not:

Step 6: Therapeutic trial of a tricyclic antidepressant (e.g. amitriptyline) or an anti-convulsant (e.g. carbamazepine or gabapentin) for pain which is more complex or difficult to control. Note that the prescriber should check the licensed indications for individual products in these classes.

Class IIb – Chronic long-term pain of a progressive nature

This group includes cancer patients and some patients with neuropathic pain e.g. diabetic patients. Treatment should follow the guidance for Class IIa chronic pain in relatively stable conditions (see above). If there is a possibility of neuropathic pain, an early trial of a tricyclic antidepressant (e.g. amitriptyline) or anti-convulsants (e.g. carbamazepine or gabapentin) should be considered at the outset. In addition, the patient should be reviewed regularly and more potent opioids, eg morphine, oxycodone or fentanyl, should be considered as soon as pain fails to respond to lower potency opioids. This is particularly likely to happen in the case of cancer

pain or some severe complex pain syndromes, where there may be a neuropathic component. Treatment of severe progressive cancer pain is not within the scope of this advice.

Medicines and Healthcare products Regulatory Agency - October 2004.