

CO-PROXAMOL UPDATE

JANUARY 2008

As of this month, co-proxamol is no longer routinely available for supply on prescription. The phased withdrawal of this product was announced by the MHRA in 2005 in order to allow sufficient time for patients to be moved to a suitable alternative.

Prescribing rates have fallen since this announcement in 2005 however in the period July to September 2007 there were 25,854 prescriptions for co-proxamol issued in the former Northern and Yorkshire region (net ingredient cost = £94,286). Therefore it is important that all remaining patients currently prescribed co-proxamol have their medication reviewed.

There will be a small group of patients who find it difficult to change, or in whom there is an identified clinical need for continued co-proxamol prescribing (where alternatives are ineffective or contraindicated). Supply for this group of patients will continue on a named-patient basis however prescribers should be aware of the implications of using unlicensed products.

PRACTICE POINTS:

- No new patients should be started on co-proxamol.
- Any existing patients should have their medication reviewed and an adequate trial of alternative pain control methods implemented.
- In the small group of patients for whom alternative medications are contraindicated or adequate trials have been ineffective, supplies of co-proxamol will continue to be available on an unlicensed, named-patient basis from Clinigen (tel no. 01283 494340; www.clinigen.co.uk).
- Patients should be informed when an unlicensed product has been prescribed. Responsibility for any adverse events associated with the use of an unlicensed product lie with the prescriber.
- The drug tariff price for 100 tablets of co-proxamol has dramatically increased from £2.79 (December 07) to £20.36 (January 08).

For further details on the MHRA decision and consultation please see the MHRA website www.mhra.gov.uk or the November 2007 Drug Safety Update Bulletin http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=1100

DRUG UPDATE

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Co-proxamol

Co-proxamol is a combination analgesic containing paracetamol and the opioid dextropropoxyphene. It is still commonly prescribed for acute and chronic pain. It has limited efficacy, and there is no evidence that the combination is more effective than paracetamol alone. Dextropropoxyphene is highly toxic in overdose and may also cause drug interactions and dependency. New prescriptions cannot be justified on efficacy and safety grounds. Alternative analgesic strategies should be actively pursued in patients receiving the drug in the long term.

What is it?

Co-proxamol is a prescription only analgesic licensed for the management of mild to moderate pain.¹ It contains paracetamol 325 mg and dextropropoxyphene 32.5 mg, a mild narcotic analgesic structurally related to methadone.¹

A study recently published by the Centre for Suicide Research concluded that self-poisoning with co-proxamol was commonly implicated in drug related suicides and suggested that the availability of co-proxamol should be reduced.²

This document reviews the efficacy and safety of co-proxamol.

How effective is it?

One systematic review assessed data from 26 double-blind randomised controlled clinical trials (n = 2231).³ These included head to head comparisons of dextropropoxyphene (65 or 100 mg) in combination with paracetamol 650 mg and paracetamol 650 mg alone, as well as three way comparisons of co-proxamol, paracetamol and placebo. The patients had post-surgical pain, arthritis, or musculoskeletal pain. The main outcome measured was the difference in pain intensity over 4-6 hours (12 hours in one study). The difference in pain intensity between co-proxamol and paracetamol was not significantly in favour of co-proxamol (95% confidence interval: -0.2 to 14.9). The authors concluded that on the basis of analgesic efficacy in both head to head and indirect comparisons there was no evidence to support prescribing co-proxamol instead of paracetamol.

Another systematic review analysing data from indirect comparisons found no significant difference between single dose co-proxamol and paracetamol alone in the management of postoperative pain.⁴

How safe is it?

The adverse effects of co-proxamol are similar to other opiates. The most frequently reported include dizziness,

sedation, nausea and vomiting. Physical and psychologic dependence is reported with dextropropoxyphene as with other narcotic analgesics.^{1,5} In patients receiving co-proxamol and warfarin concurrently INR levels should be closely monitored as co-proxamol increases the prothrombin time ratio. Because dextropropoxyphene increases plasma carbamazepine concentration, severe neurological signs including coma have occurred with concomitant use of carbamazepine.¹

Co-proxamol is very dangerous in overdose causing coma, severe respiratory depression, convulsions and cardiac arrhythmias.⁶ Death can occur after ingestion of 10 – 20 tablets especially when CNS depressants such as alcohol, sedatives and tranquillisers have also been taken.⁶

A recent study of national mortality statistics examined the incidence of fatal drug overdose involving co-proxamol, tricyclic antidepressants or paracetamol (n=4162).² When the hazard ratios of death and non-fatal presentations were compared, the risk of dying following an overdose with co-proxamol was 2.3 times greater than for TCAs (Hazard ratio 95% CI: 2.1 to 2.5) and 28.1 (Hazard ratio 95% CI: 24.9 to 32.9) times that for paracetamol. The authors suggest that the availability of co-proxamol should be restricted, large quantities should not be prescribed without good reason and patients should be instructed to return unwanted supplies to pharmacies and GP surgeries.

Between 1995 and 1998 one locality (Doncaster) identified 18 suicides involving co-proxamol.⁷ In 1998 Doncaster Health Authority asked GPs to reduce the amount of co-proxamol prescribing and Doncaster Royal Infirmary removed co-proxamol from its formulary. This resulted in a 60% reduction in co-proxamol prescribing. Since the beginning of 2000 only 5 suicides have been attributed to co-proxamol. Although the numbers are too small to demonstrate a statistical association between the amount of co-proxamol prescribed and the number of suicides these data are encouraging.

What other options are there?

If patients are receiving maximum doses of regular paracetamol and additional pain relief is required then supplemental doses of either a non-steroidal anti-inflammatory drug such as ibuprofen or an appropriate dose of a less toxic opioid such as codeine or dihydrocodeine may be helpful. Combined preparations should not normally be used because they either contain too small a dose of opioid or are too expensive. Doses should be titrated up to optimise pain relief and to minimise opioid exposure.

When should it be used?

Co-proxamol contains just 325 mg of paracetamol per tablet, with 2 tablets providing almost half the standard dose of paracetamol. There is no evidence that dextropropoxyphene in combination with paracetamol is more effective than paracetamol alone. Co-proxamol

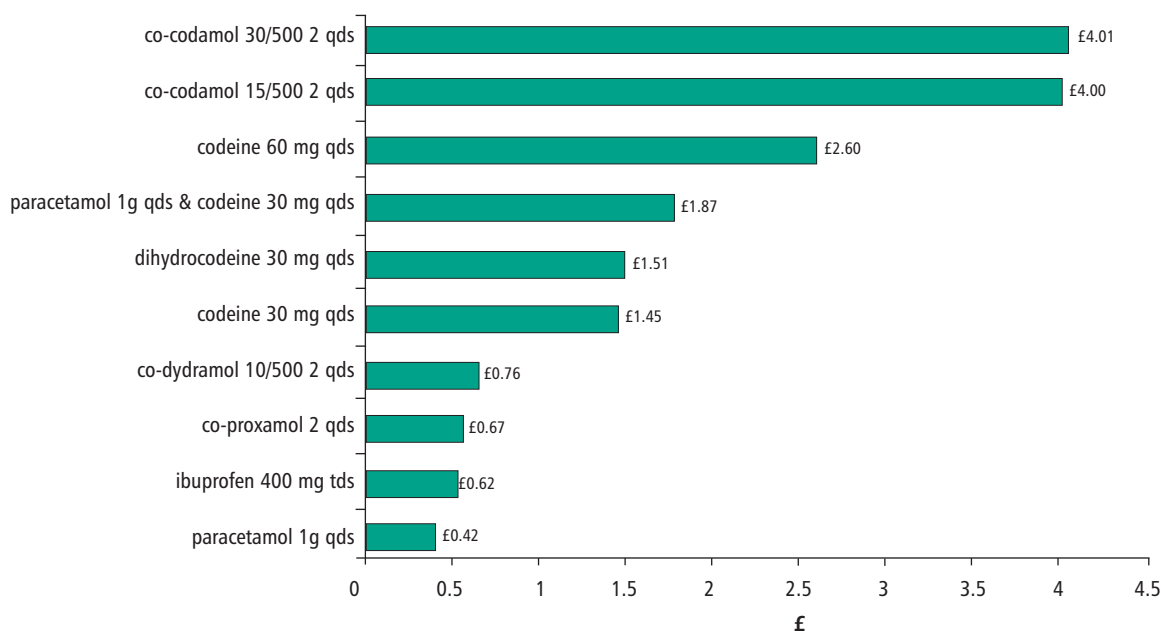
should not be used under any circumstances for patients who have not previously been taking it, based on the available efficacy and safety data. Elderly patients have an increased risk of adverse effects from all drugs and in order to reduce the risk of falls in this group of patients co-proxamol should not be prescribed.⁸ Co-proxamol is contraindicated in patients who are prone to suicide or addiction.¹ It is considered to be less suitable for prescribing by the BNF.⁵ Attempts should be made to convert patients receiving repeat prescriptions to other analgesics. Use of co-proxamol in hospitals should also be discouraged.

How much prescribing goes on?

During 2003 over 1 million prescriptions for co-proxamol were dispensed at a cost of nearly £1.5 million in the former Northern & Yorkshire Region. This represented an 8% decrease compared with the number of items prescribed during 2002.⁹

How much does it cost?

Cost for 7 days treatment (prices from MIMS/Drug Tariff April 2004)



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

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KEY RCT - randomised controlled trial, CT-controlled trial, G-guidelines, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial

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