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 SUBCOMMITTEE ON PHARMACOVIGILANCE  
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<b>TITLE OF PAPER:    RISK-BENEFIT OF CO-PROXAMOL PRODUCTS</b>	
<b>RISK: BENEFIT ASSESSMENT</b> For advice	<b>THERAPEUTIC CLASSIFICATION:</b> Analgesic
<b>LICENCE HOLDER:</b>  Several	<b>PRODUCT NAMES:</b> Co-proxamol Distalgesic
<b>ACTIVE INGREDIENT:</b> Dextropropoxyphene + paracetamol	<b>PREVIOUS CONSIDERATION BY    CSM:</b> 1985
<b>LEGAL STATUS:</b> POM	<b>CONSIDERATION BY OTHER    COMMITTEES:</b> None
<b>SALE/SUPPLY:</b> POM	

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## EXECUTIVE SUMMARY

- The purpose of this paper is for the Committee to consider the risk:benefit evaluation of co-proxamol in view of its established toxicity in overdose. The Committee's advice is sought on any indications for which the risk:benefit evaluation of co-proxamol is favourable.
- Co-proxamol is indicated for '*mild to moderate pain*' with a usual maximum daily dose of 8 tablets. It contains paracetamol and dextropropoxyphene, a weak opioid analgesic that is known to be toxic in overdose; as few as 10-20 tablets may be fatal and death most often occurs within an hour, leaving little time for rescue. Co-ingestion of alcohol or other central nervous system depressants significantly increases risk.
- Each year 300-400 people in England and Wales commit suicide or fatally overdose with co-proxamol.
- There is growing concern prompted by recently published UK research showing that co-proxamol alone now accounts for almost one-fifth of drug-related suicides and is second only to tricyclic antidepressants as an agent of fatal drug overdose. In addition, concerns raised by Sweden in the European Parliament have prompted a referral to the Pharmacovigilance Working Party.
- A key goal of the National Suicide Prevention Strategy for England is to reduce the number of suicides as a result of self-poisoning. Regulatory action has proved effective in reducing the incidence of fatal paracetamol poisoning and the Committee's advice is now sought on proportionate regulatory measures to reduce co-proxamol fatalities.
- Co-proxamol has not been subjected to modern standards of clinical research; there have been no robust studies of greater than 48 hours duration. It does not meet the European criteria for a 'fixed combination' product as there is no evidence of synergy between the active ingredients. A review of efficacy has shown that-
  - For acute pain, there is no robust evidence that co-proxamol has superior analgesic efficacy to full strength paracetamol
  - For chronic pain (>48 hours), analgesic efficacy has not been demonstrated
- Prescribers have repeatedly been warned of the unproven efficacy and proven toxicity of co-proxamol for more than 20 years but it is still widely used by hospitals and is prescribed to approximately 1.7 million GP patients annually. (see section 6.1).

## RISK:BENEFIT OF CO-PROXAMOL PRODUCTS

### 1 PROBLEM STATEMENT

The purpose of this paper is for the Committee to consider the risk:benefit evaluation of co-proxamol in view of its established toxicity in overdose. The Committee's advice is sought on any indications for which the risk:benefit evaluation of co-proxamol is favourable.

### 2 INTRODUCTION

#### 2.1 Fatal co-proxamol poisoning

The dangers of DXP overdose, especially when taken with alcohol are well established and CSM advice aimed at the prevention of suicide or fatal overdose was published as early as 1985 (Annex 1). Each year 300-400 people in England and Wales commit suicide or fatally overdose with medicines containing dextropropoxyphene (DXP), usually as co-proxamol; co-proxamol alone is estimated to account for about 18% of drug-related suicides and 5% of all suicides.

A key goal of the National Suicide Prevention Strategy for England is to reduce the number of suicides as a result of self-poisoning. Regulatory action has proved effective in reducing the incidence of fatal paracetamol poisoning and the Committee's advice is now sought on proportionate regulatory measures to reduce co-proxamol fatalities.

#### 2.2 History of co-proxamol/dextropropoxyphene

Co-proxamol is a combination of dextropropoxyphene (usually 32.5mg) and paracetamol (325mg) that is extensively prescribed for mild to moderate pain. The usual dose is two tablets or capsules 3-4 times daily. Dextropropoxyphene (brand name Doloxene) is an opioid analgesic of lesser efficacy than codeine that was developed in the 1950's. Single ingredient DXP is relatively seldom used in the UK as it cannot be prescribed on the NHS.

Co-proxamol has not been subjected to modern standards of clinical research; there have been few studies of greater than 1-week duration and there is no robust evidence that co-proxamol has superior analgesic efficacy to full strength paracetamol in acute or chronic pain. It does not meet the European guideline criteria for a 'fixed combination' product as there is no evidence of synergy between the active ingredients.

Despite the lack of robust evidence that co-proxamol is more efficacious than full dose paracetamol, many prescribers consider it to be a useful alternative to non-steroidal anti-inflammatory drugs such as ibuprofen and more potent opioids in situations where paracetamol alone is ineffective. Co-proxamol is widely used by general practitioners and pain clinics for the treatment of osteoarthritis, neuropathic pain and the pain of cancer. It is often routinely initiated in hospital patients for the management of postoperative pain.

### 3 REGULATORY BACKGROUND

#### 3.1 Licensing status

There are 18 UK licences for co-proxamol and a single licence for dextropropoxyphene<sup>1</sup>; details of formulation and indications are given at Annex 2. Co-proxamol and single constituent dextropropoxyphene products were both on the market long before UK licensing began (DXP has been marketed since the late 1950's), and were given Product Licences of Right. The first full licences granted in the UK were for dextropropoxyphene in 1980 (Eli Lilly) and for co-proxamol in 1978 (Cosalgesc tablets, Cox Continental Inc.). PL 00006/ 5000R Distalgesc Tablets was granted a reviewed licence on 5/9/1980. All 18 products are subject to UK national licences and are classified as prescription only medicines (POMs). DXP as a single constituent is not available on the NHS.

##### 3.1.1 Indications

All 18 products are indicated for *mild-to-moderate pain*.

##### 3.1.2 Posology

The usual daily dose of co-proxamol is 2 tablets three or four times per day in adults and the elderly.<sup>2</sup>

Use in children is not recommended

##### 3.1.3 Pack size

Co-proxamol tablets are licensed in packs ranging from five tablets upwards to 1,000 tablets per pack (bulk packs) depending on the licence. Six products are licensed only in packs of 100 tablets. The current average quantity per prescription is 100 tablets (14 days' treatment).

Dextropropoxyphene napsylate is licensed in packs of 100 capsules only.

### 3.2 UK concerns

The risk-benefit of co-proxamol has been discussed in the UK literature for a number of years. The main concerns were whether or not co-proxamol was, in fact, any more effective than paracetamol alone and its narrow safety margin in overdose. In 1985 Current Problems in Pharmacovigilance addressed the topic "Death with dextropropoxyphene", including the role of alcohol (Annex 1). CSM advice at that time was:-

- RESTRICT the number of tablets prescribed at any one time to the smallest quantity necessary for the condition being treated
- AVOID prescribing DXP-containing medicines for patients who were

<sup>1</sup> February 2005 Update: There are currently 14 product licences for co-proxamol. Dextropropoxyphene is no longer marketed.

<sup>2</sup> Five out of 17 licences for co-proxamol state that the maximum daily dose is eight tablets. The usual daily dose of dextropropoxyphene is 100mg DXP napsylate (equivalent to 65mg DXP HCl) three or four times per day

believed to be at risk of self-poisoning or those with a history of alcohol abuse

- ADVISE patients that the tablets are for their use only; the recommended dose must not be exceeded; that the drug can be extremely dangerous if taken with alcohol or CNS depressants and that unwanted tablets should be destroyed.
- INFORM patients that they should be given a patient information leaflet at the point of dispensing and to ask for one if it is not offered.

More recently, in May 2003, Professor Keith Hawton and colleagues from the Centre for Suicide Research at Oxford published the results of a study examining the role of co-proxamol in deliberate self-poisoning. (Annex 3). Co-proxamol alone accounted for 18% of drug-related suicides in England and Wales during 1997-1999 in individuals aged 10 years and over, compared with 22% with tricyclic anti-depressants alone and 9% with paracetamol alone. A related investigation of 123 co-proxamol poisoning suicides by the same authors is currently in publication. The forthcoming publication discusses some of the options for preventing fatal co-proxamol overdose that CSM is asked to consider at section 8 of this risk:benefit assessment.

### 3.3 European Parliamentary Question (oral) of 21 May 2003

The Scandinavian journalists, Drs Birgitta and Ulf Jonasson have been studying deaths in Sweden involving DXP-containing products for several years (Annexes 4 and 5). They have projected the Swedish figures (approximately 200 deaths per year amongst a population of ~8.7 million ) to estimate that there could be as many as 2,000 deaths per year involving DXP-containing products in the UK (five-fold greater than the observed UK mortality), and a similar death rate in France. The Jonassons have contacted national regulatory authorities including the MHRA regarding these concerns.

#### **Assessor's comment:**

*Swedish data cannot be extrapolated to other countries. National prescribing patterns for analgesics and CNS depressants, the prevalence of drug abuse and alcohol consumption and differing population structures will produce major international variations in patterns of DXP-related deaths. Key differences between the UK and Sweden are that single constituent DXP is widely used in Sweden whilst the NHS prescribing 'blacklisting' has virtually eradicated its use in the UK and that in Sweden DXP is used for detoxification of opiate addicts and is frequently a drug of abuse.*

The Jonassons have been conducting a high-profile campaign on the dangers of DXP, which led to discussion of one of their publications at the Pharmacovigilance Working Party (PhVWP) in February 2003. Their campaign prompted an oral Parliamentary Question in the European Parliament (21 May 2003) by Euro MP Mrs Marit Paulson (Sweden) on the dangers of DXP (OQ 10/02). This specifically asked if the Commission was aware of these dangers, if any action had been taken and if the Commission was prepared to initiate a study on the topic. This matter was

referred to PhVWP and they are currently evaluating the risks of DXP on behalf of the European Commission.

### 3.4 Misuse of Drugs Act 1971 and Misuse of Drugs Regulations 2001

Dextropropoxyphene and co-proxamol are not "controlled drugs". DXP is currently listed under Schedule 5 of the Misuse of Drugs Regulations 2001ss. For DXP this means any oral preparation containing not more than 135mg DXP base/ dosage unit (or with a concentration of not more than 2.5% of base in undivided preparations) is exempt from virtually all controlled drug requirements, other than retention of invoices for two years.<sup>3</sup>

## 4 CLINICAL PHARMACOLOGY AND TOXICOLOGY

### 4.1 Clinical pharmacology

DXP is a synthetic opioid analgesic, with structural similarity to methadone. It binds primarily to  $\mu$ -opioid receptors and produces analgesia and other CNS effects similar to those seen with morphine-like opioids. As an analgesic 90-120mg of DXP HCl administered orally would equal the analgesic effects of 60mg codeine<sup>4 5</sup>. (NB a standard dose of co-proxamol contains only 65mg of dextropropoxyphene)

DXP is detectable in plasma 15-30 minutes after oral ingestion<sup>6</sup>. It is subject to extensive first pass metabolism in the liver and its main and active metabolite is norpropoxyphene (NXP), produced by N-demethylation. DXP is rapidly distributed and concentrated in the brain, liver, lungs and kidneys. Peak plasma concentrations occur within 1-2.5 hours of ingestion. Equimolar doses of DXP HCl and DXP napsylate produce similar plasma concentrations. After therapeutic doses plasma concentrations are in the range 0.06-0.75mg/l. In severe hepatic dysfunction, the plasma concentration of DXP is increased whilst that of NXP is reduced.

Both DXP and NXP are lipid soluble and have long half-lives, 15-24 hrs for DXP and 23-34 hrs for NXP<sup>7</sup> or longer. With three times daily dosing, both DXP and NXP accumulate for at least 4 days, after which the plasma concentrations are 5-7 times higher than those observed following a single dose. Repeated doses of DXP at 6-hourly intervals lead to increasing plasma concentrations with a plateau after the ninth dose at 48 hours<sup>8</sup>. The half-lives of DXP and NXP are prolonged in the elderly.

There is great variability between subjects in the rate of clearance and of plasma concentrations achieved. DXP is excreted in the urine, mainly as metabolites. In

<sup>3</sup> <http://www.hmso.gov.uk/si/si2001/20013998.htm>

<sup>4</sup> Goodman & Gilman's The Pharmacological Basis of Therapeutics, 2001, Tenth edition,

<sup>5</sup> Therapeutic drugs, 1999, Second edition, ed. Dollery, C. Publ. Churchill Livingstone, Edinburgh

<sup>6</sup> Drugs & Therapeutic Bulletin 21(5) (1983) 17-19. Distalgesic and its equivalents: Time for action

<sup>7</sup> Haigh, S. 34 (1996) 1840-1841 The Lancet 12 years on: co-proxamol Revisited

<sup>8</sup> PL 00006/5086R

patients with poor renal function (GFR <10ml/ min) elimination is prolonged and plasma concentrations increase such that dose adjustment may be necessary.

#### **4.2 Rationale for co-proxamol as a compound analgesic**

There is no evidence that paracetamol and DXP have synergistic effects. In theory, the combination of DXP and paracetamol offers the possibility of enhanced analgesic efficacy by combining two drugs with differing modes of action and different onsets and durations of action. Another argument for co-proxamol would be that the combination of lower dose of the two drugs reduces the toxicity attributable to a full dose of either constituent. An additional advantage is simplicity of dosing which may be of benefit to patients receiving multiple medications. But paracetamol at full strength is not associated with serious side effects so there is little to be gained from reducing the dose.

The fixed dose combination contains a relatively low dose of paracetamol (two co-proxamol tablets normally contain 650mg of paracetamol) and this may be subtherapeutic. An added disadvantage is that there is no flexibility for dose titration of the individual elements.

#### **4.3 Toxicity**

The fatal blood level of dextropropoxyphene is difficult to estimate from post mortem specimens because the drug is lipid soluble and rapidly distributed within the tissues. According to TOXBase, the fatal dose of DXP may be as little as 10 capsules (equivalent to 65mg DXP HCl each) for an adult, especially when CNS depressants such as alcohol, sedatives and tranquillisers have also been taken. Alcohol with co-proxamol is a particularly hazardous combination. The toxic dose will vary greatly between individuals; the high blood levels tolerated by a patient receiving co-proxamol for chronic pain may prove fatal to a treatment-naïve person and chronic abusers of co-proxamol may take much larger doses without developing toxicity. Like other opioids, DXP and NXP depress respiration, but unlike other opioids, they also prolong atrio-ventricular conduction and slow the heart rate (Annexes 6, 7). In animals, the cardiac effects cannot be reversed by naloxone. This effect on QRS interval appears to be dose dependent (Bateman, Annex 8) and may explain why overdose with co-proxamol is more likely to be fatal than other opioids. Furthermore, as DXP is rapidly absorbed from the GI tract, cardiac and respiratory effects appear early, with death occurring within 1 hour of ingestion so many patients die before hospital admission.

Signs and symptoms of overdose with DXP include coma, severe respiratory depression, convulsions, and cardiac arrest within 30 minutes of overdose, especially if alcohol has also been taken. Cardiac arrhythmias including torsade de pointes may occur up to 12 hours after ingestion, particularly if features of CNS depression are also present. In less severe cases pallor, nausea and vomiting may persist for about 24 hours.

##### **4.3.1 Interaction of DXP with alcohol**

In healthy volunteers the concomitant intake of alcohol increased the bioavailability of an oral dose of DXP (130mg) by a mean of 25% (Annex 9), by reducing first pass metabolism. In addition to this pharmacokinetic interaction the dangers of taking alcohol with DXP may be in part due the additive effects of respiratory depression caused by both drugs. Young and Lawson (1980, Annex 10) found that 20 tablets of co-proxamol may be fatal when taken with alcohol or any other CNS depressant drugs. Of greater concern, Whittington & Barclay (1981 Annex 11) found that as few as 6-15 tablets of co-proxamol could be lethal when taken with alcohol.

In a study in Sweden reviewing deaths classified as non-suicidal (i.e. accidental plus intent unknown), Jonasson et al (2000, Annex 4) found that of all groups, middle-aged men who are habitual or social drinkers receiving medication for pain were most at risk of non-suicidal death due to co-ingestion of DXP-containing products with alcohol.

**Assessor's comment:**

*It is of great concern that avoidable accidental deaths may occur due to lack of awareness of the dangers of taking DXP with alcohol.*

#### 4.4 Dependence/Abuse

The potential for DXP abuse and dependence has been documented repeatedly, with reports first appearing the 1960s and 1970s (Annex 5). Of particular concern was the high regular usage (second only to heroin) amongst adolescents admitted to drug abuse programmes. Addiction may often be iatrogenically induced and maintained, especially in chronic pain syndromes, with many physicians not fully aware of the potential for abuse and addiction with DXP, or possibly unaware that DXP is an opioid. A review comparing medico-legal reports of fatal overdoses amongst drug addicts in the Nordic countries (Denmark, Sweden, Norway and Finland) in 1991 and 1997 (Annex 12) showed that DXP was cited as a main cause of death in all 4 countries, especially Sweden and Finland.

There have been no specific reports to the MHRA Inspection and Enforcement Division of illegal activity involving dextropropoxyphene and / or co-proxamol but like other prescription medicines, co-proxamol is now readily available via the internet<sup>9</sup>.

There have been 6 spontaneous UK ADROIT reports directly citing DXP abuse/dependence type reactions on ADROIT since 1995. Two cases involved the single constituent product Doloxene.

**Assessor's comment:**

*Single-constituent DXP is widely used in other countries but it is not prescribable on the NHS so relatively little used. This may limit the potential for a widespread abuse in the UK.*

<sup>9</sup> Dr Fabrizio Schifano and Dr Paola Deluca (St George's Hospital Medical School) under the auspices of the Psychonaut 2002 Project (an EU-funded programme looking at sales of drugs over the internet)

## 4.5 Current warnings in UK SPCs and Patient Information

### 4.5.1 Standard paracetamol warnings

Under SI 3105/1998, all paracetamol-containing products are required to include the overdose warnings on the labelling and in the leaflet:

<p style="text-align: center;"><b>Statutory labelling requirements</b> <i>(products intended for use by adults and children over 12 years)</i></p> <ul style="list-style-type: none"><li>• The boxed warning <div style="border: 1px solid black; padding: 2px; text-align: center;"><b>Do not take with any other paracetamol-containing products</b></div></li><li>• The boxed warning <div style="border: 1px solid black; padding: 2px; text-align: center;">Immediate medical advice should be sought in the event of an overdose, even if you feel well.</div><p style="text-align: center;"><i>(products with an accompanying leaflet) or</i></p><div style="border: 1px solid black; padding: 2px; text-align: center;">Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage</div><p style="text-align: center;"><i>(if no accompanying leaflet)</i></p><p style="text-align: center;"><b>Statutory leaflet requirement</b> <i>(products intended for use by adults and children over 12 years)</i></p></li></ul> <ul style="list-style-type: none"><li>• Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.</li></ul>
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### 4.5.2 SPCs

An example of a SPC for co-proxamol is given in Annex 13. Key information in the SPCs of all 18 currently licensed products is not uniform:

<p><b>Alcohol</b> In 17 products the advice is to avoid alcohol and in the other, co-ingestion of alcohol with excessive doses of DXP is mentioned as one of the major causes of drug-related deaths.</p> <p><b>CNS Depressants</b> All licences warn of the risk of concomitant use of CNS depressants to varying degrees. Some merely say that the effects may be additive to those effects of DXP whereas, some include the much stronger "<i>Excessive doses of DXP, either alone or in combination with depressants of the CNS (including alcohol) are a major cause of drug-related deaths. Fatal effects can occur within 15 minutes and are not uncommon within the first hour of overdosage. Some deaths have occurred as a result of excessive ingestion of [product] alone or in combination with other drugs.</i>"</p> <p><b>Mental illness, suicidality and addiction</b> Nine licences contain the contra-indication of patients who are suicidal or addiction-prone; four other licences contain the precaution of use in patients with a</p>
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psychological or personality disorder and one licence contains both statements.

#### **Renal and hepatic impairment**

Most licences advise caution or dose reduction in renal or hepatic impairment (three caution in severe renal or hepatic impairment) while some advise use of the adult dose in the elderly and others advise dose reduction in the elderly.

#### **4.5.3 Label**

Most but not all cartons carry a warning for alcohol such as "Avoid alcohol" (e.g. Annex 13), but some carry no warning at all. Other label warnings include "Do not exceed the stated/ recommended/ prescribed dose".

#### **4.5.4 Patient Information Leaflets**

The PILs carry more warnings and these tend to be more detailed than the labelling. For example, for the alcohol warning, the PIL for PL 00152/0255 (Annex 13) states "Do not drink alcohol whilst taking this medication as it may dangerously increase the effect of the tablets." Others state "Do not drink alcohol whilst taking [product]. It can be very dangerous." or similar. For the other warnings discussed above, this PIL includes "Have you ever been an alcoholic or drug addict? Are you taking any ...anti-depressants" - if the answer is YES do not take these tablets." Other PILs contain a longer list of CNS-depressant drugs as a caution and the contra-indications of suicide and drug addiction have been translated as "Tell the doctor if you suffer from depression or any other psychiatric condition."

#### **Assessor's comment:**

*The product information for co-proxamol and all DXP containing products should contain a set of standard warnings that clearly and strongly convey the CSM advice of 1985. In order to prevent unintentionally fatal overdose by the patient or impulse parasuicide by other household members, key messages must be emphasised in the PIL and label:*

- *Never take with alcohol*
- *Never take more than the prescribed dose*
- *Dispose of any unused medicine as soon as possible*

## **5 EVIDENCE OF EFFICACY**

Dextropropoxyphene and co-proxamol were developed in the 1950/60s and their efficacy has not been investigated to current standards. There is very little evidence that DXP or co-proxamol have a greater analgesic effect than paracetamol alone and there is no evidence of a synergistic effect. Therefore, co-proxamol does not meet the current European guideline criteria for a 'fixed combination' product. Furthermore, most evidence on the efficacy of analgesics is based on single-dose studies in acute pain, mostly post-operative pain (Annexes 7, 14, 15,16).

## 5.1 Acute pain

There have been very few controlled clinical comparisons of co-proxamol versus low dose paracetamol alone or DXP alone, and most have been single-dose studies. Data from randomised controlled clinical studies have been reviewed in two systematic reviews, described below.

### 5.1.1 Acute moderate pain

In 1997, Li Wan Po and Zhang (Annex 15) reviewed data from 24 randomised, double-blind single oral dose clinical trials, evaluating whether DXP HCl (65mg or 100mg) in combination with 650mg paracetamol (DXP+P) was more effective than paracetamol 650mg alone for moderate pain. The review covered over 2000 patients receiving medication for post-partum or musculoskeletal or arthritic pain or for pain following various types of surgery. Outcomes measures were difference in pain intensity over 4-6 hours (12h in one study), response rate ratio (at least moderate pain relief) and difference in response rate. Most of the trials were placebo controlled, so two independent sub-meta-analyses were used to produce indirect comparisons between treatments. The indirect comparisons showed that both paracetamol alone and DXP+P had significantly greater efficacy than placebo, but there was no difference between the two active treatments. The three trials where direct comparisons were used (N=301 patients) also showed that the effects of the combination of DXP+P were not significantly different from those of paracetamol alone for pain intensity or rate response ratio. However, the authors commented that any small additive effect of DXP may have been missed because of the low numbers of [quality] studies which could be included.

### 5.1.2 Moderate-severe post-operative pain

In 1998 Collins et al (Annex 16) published a similar systemic review of single-dose trials comparing DXP (DXP HCl 65mg) versus paracetamol 650mg plus DXP (65mg HCl or 100mg napsylate (equivalent)) for moderate-to-severe post-operative pain. Of 130 articles identified, only 6 reports could be used for DXP (440 patients, 214 receiving DXP) and only 5 reports could be used for DXP+P (963 patients, 478 receiving DXP+P). Outcome measures were summed pain intensity and pain relief data, converted to the number of patients with at least 50% pain relief, to allow a common measure to be used between trials. Indirect comparisons were made as the trials were placebo controlled. Both DXP and DXP+P showed significantly greater efficacy than placebo (number needed to treat for one patient to achieve at least 50% pain relief versus placebo were 7.7 for DXP and 4.4 for DXP+P. Confidence intervals overlapped). No direct comparison was made with paracetamol.

**Assessor's comment:**

*In the UK, co-proxamol and DXP are both indicated for mild-moderate pain but their use in this indication has not been adequately investigated as the studies discussed above have mostly evaluated efficacy in moderate or moderate-severe pain. Furthermore, analgesic efficacy in pain associated with acute surgical/obstetric trauma in relatively young patients may be very different to the efficacy that may be achieved with other types of pain and in older patients.*

*For acute moderate pain, there is no robust evidence that co-proxamol is more effective than paracetamol alone.*

*For acute moderate-severe pain, there is some evidence that co-proxamol has greater efficacy than DXP alone and both have greater efficacy than placebo. No robust comparison has been made between co-proxamol and full strength paracetamol.*

## **5.2 Chronic pain**

The efficacy of co-proxamol in chronic use has rarely been studied and extrapolation of the results of short-term or single dose studies to chronic or regular use is clearly inappropriate. DXP and its active metabolite norpropoxyphene both have long half-lives (15-24 hours and 23-34 hours respectively) and there is potential for accumulation over a number of days, with gradual build up to plasma levels 5-7 times greater than that achieved with a single dose. It is possible that a full therapeutic effect can only be achieved with chronic dosing of co-proxamol and therefore it may have a role in treating chronic pain.

Li Wan Po and Zhang (Annex 15) identified two repeat dose studies during their review which failed to demonstrate a beneficial effect of DXP+P over paracetamol but the studies only lasted for 48 hours, which might not fully represent chronic dosing.

The Drugs and Therapeutic Bulletin (1983 Annex 6) cites an Australian double-blind cross-over study (Owen and Hills, 1980) which compared 1g paracetamol against 650mg paracetamol plus 65mg DXP for one week each in rheumatology patients. Significantly more patients preferred the combination (the authors state that the reason for this preference was not clear) and no withdrawal symptoms were detected.

In the experience of some specialists in pain management, pain not controlled by regular dosing with paracetamol alone is relieved by repeat doses of co-proxamol (Annex 17). Patients who attend pain clinics have often tried several compound analgesics and, for some of these, co-proxamol is the most effective therapy, which may reflect a neuropathic component to their pain that is different to post-operative pain (Annex 18).

### **Assessor's comment:**

*It is theoretically possible on pharmacokinetic grounds that co-proxamol may only have a full therapeutic effect with chronic dosing. However, there are no robust published studies of greater than 48 hour duration and efficacy in chronic use has not been demonstrated.*

*Poor analgesic efficacy is a cause for concern as it may prompt patients to intentionally overdose (e.g. by increasing frequency of dosing) in an attempt to achieve adequate pain relief. ONS mortality statistics do not identify this patient group as they count fatal overdoses of unknown intent as suicides.*

### 5.3 Reasons for the extensive use of co-proxamol

Doctors unquestioningly prescribe co-proxamol because it has been extensively used for decades. They may favour it because it is less constipating than co-codamol and has none of the major hazards of NSAIDs but much of the widespread prescribing by both hospital doctors and GPs is due to custom and practice. It is possible that patients like taking co-proxamol because the narcotic side effects of DXP make them feel better (e.g. mild euphoria or sedation affords them a good night's sleep and some relief from the anxiety of terminal illness or chronic pain). In patients already taking NSAIDs, co-proxamol may be a convenient adjunct.

In a 1996 survey by Haigh of 30 UK teaching hospitals (Annex 7) co-proxamol accounted for 35% of all issues of paracetamol-containing medicines (paracetamol 500mg accounted for only 27%). This could not fail to have a major impact on the future prescribing habits of students and junior doctors.

According to Goodman and Gilman<sup>10</sup>, "*The wide popularity of propoxyphene in clinical situations in which codeine was once used is largely the result of unrealistic concern about the addictive potential of codeine*". There is a common belief amongst doctors and nurses that two tablets of co-proxamol contain a full 1g dose of paracetamol. Even if doctors are aware that co-proxamol has not proven to be more efficacious than full strength paracetamol alone, the dynamics of the doctor-patient relationship can make it difficult to prescribe simple analgesics when something more potent is expected. Under these circumstances prescribing 'just paracetamol' might be interpreted as a disregard of the patient's perceived pain and suffering.

### 5.4 Treatment guidelines

- The WHO analgesic ladder for managing cancer pain<sup>11</sup> follows a 3-step model: "*If pain occurs, there should be prompt oral administration of drugs in the following order: nonopioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. To calm fears and anxiety, additional drugs – "adjuncts" – should be used. To maintain freedom from pain, drugs should be given "by the clock", that is every 3-6 hours, rather than "on demand".*"

This three-step model has been widely adopted in local guidelines with co-proxamol positioned at Step 2.

Critical reviews of the evidence for co-proxamol/DXP do not recommend them.

- A MeReC bulletin article on the Use of oral analgesics in primary care (2000; Annex 14), including co-proxamol and DXP, recommends that analgesics should be prescribed step-wise, tailored to the individual by titration and subject to regular review but advises against the use of co-proxamol due to concerns about safety and efficacy.

<sup>10</sup> Goodman & Gilman's The Pharmacological Basis of Therapeutics, 2001, Tenth edition

<sup>11</sup> <http://www.who.int/cancer/palliative/painladder/en/>

- Drugs and Therapeutic Bulletin (1998 Annex 19) advises that there is little evidence to support prescribing DXP+P for acute pain, such as that following surgery, in preference to paracetamol alone, although the position for prolonged use is not clear.
- The British National Formulary regards co-proxamol as 'less suitable' and warns against the dangers of dextropropoxyphene overdose<sup>12</sup>.

## 5.5 Alternative analgesics

Other than full strength paracetamol, alternative drugs for mild-moderate pain include other paracetamol-opioid combination products, weaker opioids alone or NSAIDs. In principle, combination products should not be prescribed until titration of the individual constituents has established the optimal dosage for each of them.

The disadvantage of other weak opioids such as codeine and dihydrocodeine is that they tend to be more constipating than DXP (this would be undesirable in postoperative patients and in long term use). Paracetamol combinations with lower dose codeine (8mg) or dihydrocodeine (10mg) contain sub-therapeutic doses and may under-treat the pain. Paracetamol combinations with full doses of codeine or dihydrocodeine, are more constipating than DXP-containing products and are also dangerous in overdose. A further consideration is that codeine is more likely than DXP to cause opioid use disorders in chronic pain patients (Annex 5).

The use of NSAIDs is limited by their adverse events, especially gastrointestinal reactions, which may lead to fatal bleeds, particularly in the elderly. Langman (2003 Annex 20) estimates that the number of cases of bleeding ulcer attributable to NSAIDs in the UK is currently around 2,400, and that substitution of ibuprofen (2.4g/day) for other NSAIDs would reduce attributable mortality to 80 cases. Risk factors include old age and use of anti-coagulants or steroids. NSAIDs can also cause fluid retention and deterioration of renal function. CSM advice is to start on the lowest dose of the lowest risk agent and take for the shortest time.

In 1997 Collins et al (Annex 16) reviewed published studies of *single-dose* DXP or co-proxamol and other analgesics for moderate-to-severe post-operative pain. For each drug they calculated the number needed to treat (NNT), i.e. the number of patients that would need to take the drug in order to achieve at least 50% pain reduction in one of them. A number of drugs were studied but the only drug whose CI did not overlap the lower CI limit for co-proxamol was ibuprofen 400mg. The authors' other main conclusion was that co-proxamol has a similar analgesic efficacy to tramadol but has a lower incidence of adverse effects such as somnolence, dizziness, nausea and vomiting.

A new combination product of paracetamol (325mg) and tramadol (37.5 mg) has recently been approved through the Mutual Recognition Procedure (UK licence granted September 2003). There is currently no clinical experience with this product in the UK. However, as this product is indicated for moderate-to-severe pain and is for use "no longer than is strictly necessary", requiring regular monitoring if repeated

<sup>12</sup> BNF 46 September 2003 pp 210 and 212

use or long-term treatment is required, it is not a viable alternative to DXP/ co-proxamol.

**Assessor's comment**

*There is no obvious drug of choice for mild-to-moderate pain. There is no clinical situation in which co-proxamol could be considered a first-line analgesic.*

*A rational strategy would be to exhaust the therapeutic possibilities of full strength paracetamol before either switching to ibuprofen (if appropriate) or adding a mild opioid such as codeine or dihydrocodeine.*

*Many co-proxamol users are elderly and long term NSAIDs may not be a safe alternative for them.*

*Although compound analgesics should in principle be avoided as there is no flexibility of dosing, it might be argued that combination with paracetamol reduces the abuse potential of weak opioids and simplicity of dosing is valuable in the elderly and chronic sick.*

**5.6 Potential drawbacks of restricting co-proxamol usage**

The Australian experience (Shenfield, 1980, Annex 21) has shown that if co-proxamol usage is restricted, other analgesics will be used instead. The increased use of alternative analgesics will inevitably lead to an increased incidence of ADRs associated with these drugs, possibly including fatal overdose by the patient or other household members.

Some patients may benefit from the non-analgesic properties of DXP. If the alternative analgesics do not have the same narcotic side effect profile as DXP, patients experiencing mild anxiety, depressed mood or poor sleep may require an anxiolytic, antidepressant or hypnotic sedative to relieve their symptoms. Every additional drug carries an additional burden of risk.

Patients with chronic pain who are well established on co-proxamol may be unable to find a satisfactory alternative and therefore suffer an increased burden of misery.

**6 RISK ASSESSMENT**

**6.1 UK usage data**

An estimate of usage (total patient days) in England has been made by summing the UK hospital dispensing data<sup>13</sup> and the community dispensed prescriptions in England. Usage of the DXP single-constituent product was constant at ~95,000

<sup>13</sup> Hospital use is low compared with community prescribing so the extra data from Wales, Scotland and N Ireland do not have a major impact

patient days per year between 1999 and 2001, dropping to 87,350 patient days per year in 2002. Figures for co-proxamol declined each year from 187 million patient days per year in 1999 to 164 million patient days per year in 2002.

In summary:

- Co-proxamol usage is approximately 2000-fold greater than DXP usage.
- Community dispensing (i.e. GP prescribing) is 40-fold greater than hospital use.
- Community dispensing in England is sufficient for 400,000 people to take three doses of co-proxamol every day. As many people do not take a full dose every day and unused medication tends to be retained for possible future use, the number of homes where co-proxamol is available is probably several times greater than this.
- Approximately 1.7 million people per year receive prescriptions for co-proxamol, mainly for chronic musculoskeletal conditions

### 6.1.1 Hospital dispensing (UK)

Hospital usage data were obtained for 1999-2002 for the whole of the UK. The data could not be split into subsets by age. These data are based on accurate information for 96% of the population which is then arithmetically corrected to account for the missing 4%. The fall in co-proxamol usage during this period cannot be attributed to a general displacement of hospital dispensing into primary care as during the same period hospital usage of paracetamol has increased.

*Table 1: hospital dispensing*

*The daily defined dose (DDD) of co-proxamol is 6 tablets or capsules and the DDD of paracetamol is 3g*

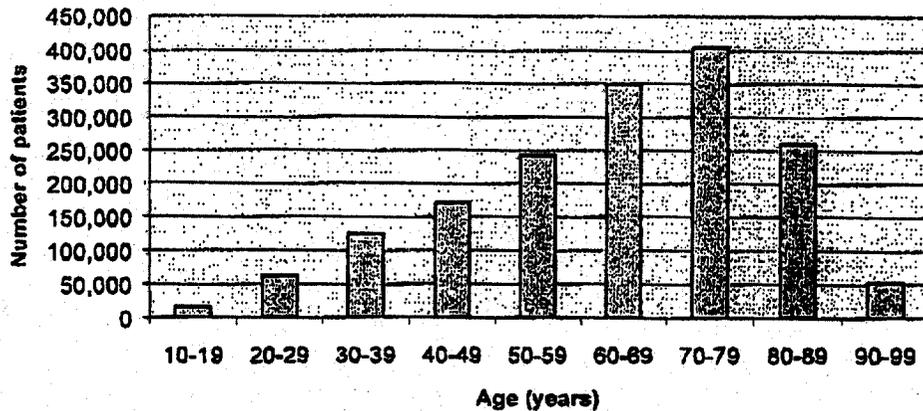
Hospital (million DDDs)	1999	2000	2001	2002
Co-proxamol	5.936	4.9085	4.0416	4.1963
DXP	0.0043	0.0027	0.0039	0.0039
Paracetamol	17.4635	21.6336	25.5555	36.1080

### 6.1.2 GP prescribing data (UK) 12 months from 1/10/2002

The Disease Analyzer - Mediplus database records all prescribing in a large sample of GP practices covering 3.5 million patients. These data are then projected to provide an estimate of prescribing in the whole UK population. The data are subject to distortion by local variations in prescribing practice and projections will significantly magnify this distortion. A total of 1.7 million patients received prescriptions for co-proxamol during the 12-month period. Approximately 1200 patients received prescriptions for DXP, too small a number to display in Figure 1 (below) which shows the age-distribution of patients receiving co-proxamol.

- e. ~~Adults aged 20-59 years~~ (anybody who has not ticked the boxes on the back of
- Children and adolescents (children under 16; persons aged 16, 17 and 18 years in full time education)
  - Adults aged 20-59 years (anybody who has not ticked the boxes on the back of the prescription form in order to claim exemption due to age or ongoing education)

**Age distribution of GP patients issued with a prescription for co-proxamol 01/10/2002-30/9/2003**



Disease Analyzer - Mediplus is not designed to yield accurate information on the duration of therapy for each recorded indication but it appears that fewer than 5% of GP patients were given co-proxamol for malignant disease and the vast majority of prescribing was for apparently chronic musculoskeletal conditions, especially arthritic and spinal problems.

These data have been obtained from the IMS Disease Analyzer - Mediplus database and the Hospital Pharmacy audit (HPA)  
 The Disease Analyzer - Mediplus database contains anonymised computerised longitudinal records of patients' GP consultations and treatment. The practices are intended to be representative of the geographical distribution of GPs in the UK and the figures can be projected up to estimate UK numbers. The database contains the records of around 2.1million patients of which half are currently active.

**HPA data**  
 This is volume data and gives the number of packs dispensed in UK NHS pharmacies. This data has been projected to UK wide figures from a coverage of over 90% of UK NHS hospitals. It does not include data from private, prison or military hospitals.

Numbers calculated by the MHRA using IMS Disease Analyzer – Mediplus September 2003

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**6.1.3 Community pharmacy data 1995-2002 (England)**

English community pharmacy data are available from 1995-2002 and since 1999 they have been available split into three age-bands according to the patient's entitlement to free prescriptions:

- Children and adolescents (children under 16; persons aged 16, 17 and 18 years in full time education)
- Adults aged 20-59 years (anybody who has not ticked the boxes on the back of the prescription form in order to claim exemption due to age or ongoing education)

- Elderly (over 60 years)

Co-proxamol community use ( patient days x1000)				
	1999	2000	2001	2002
Children	567	533	450	433
Adults	79195	59350	49455	46050
Elderly	101190	112542	116210	113041
<b>Total</b>	<b>180952</b>	<b>172425</b>	<b>166115</b>	<b>159524</b>

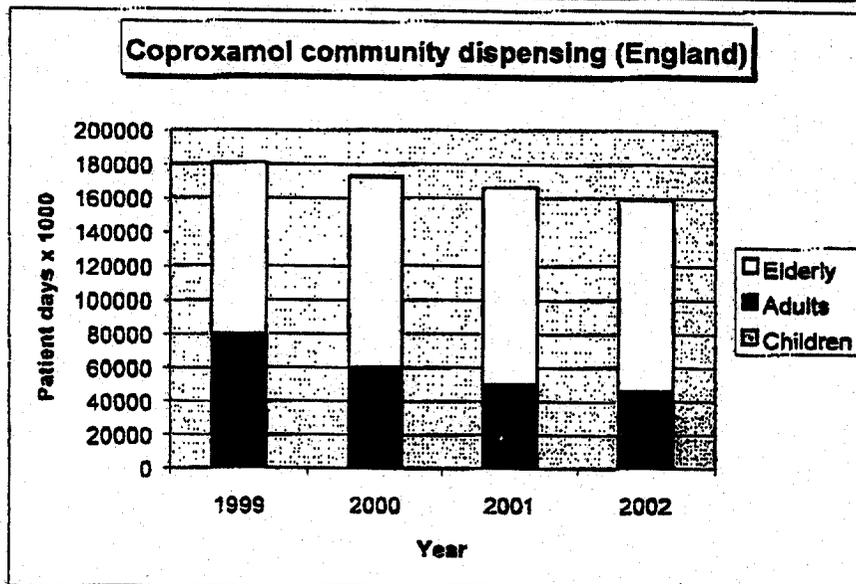


Figure 2: NB Single constituent DXP dispensing is 2000-fold lower and cannot be shown on the same chart. Use in children is also too small to be visible on this chart.

The usage of single constituent dextropropoxyphene has been approximately 2000-fold lower (~80,000 – 94,000 patient days per year). There has been no real pattern to DXP usage, the latest available figure being 83,439.2 patient days for 2002. The level of prescribed use of DXP and of co-proxamol in children and adolescents is very low, being zero for single-constituent DXP

## 6.2 Mortality and morbidity

### 6.2.1 ONS Mortality data (England and Wales)

The Office of National Statistics, UK (ONS) mortality data were extracted for 1993-2001, using specific drug names and synonyms. A split by age and sex was obtained but the figures were too small for meaningful analysis – consequently a crude age banding was used which relates to the information on age available from

the prescription data (Table 4). The drug fields were not split further, so this data set represents all cases (single or multi-poisonings, including alcohol) where DXP-containing products were mentioned as contributing to death. The figures presented are for accidental poisonings and for the sum of intentional self-poisoning plus intent unknown, which ONS recommends using for estimates of suicides. In addition, ONS figures assume that where there was a single mention of DXP it was derived from co-proxamol, because the level of prescribing of DXP single-constituent products in England and Wales is so low.

There are between 300 and 400 deaths in England and Wales each year where DXP-containing products judged to cause or to contribute to the death. The majority of these are suicides or open verdicts, with approximately one fifth being due to accidental poisonings. The actual figures for accidental deaths fluctuate from year to year, although some deaths given an open verdict (intent unknown) may be due to accidental overdose.

*Table 4: ONS mortality data by age (based on age bands available from Prescription data) Number of drug-related poisoning deaths where dextropropoxyphene, Distalgescic, co-proxamol or Doloxene was mentioned by sex, age and coroners verdict, England & Wales, 1995-2001*

<b>ABSOLUTE MORTALITY</b>									
<b>Intentional self-poisoning (ICD-9 E950.0-E950.5: ICD-10 X60-X64) plus Undetermined intent poisoning (ICD-9 E980.0-E980.5: ICD-10 Y10-Y14)</b>									
	1993	1994	1995	1996	1997	1998	1999	2000	2001
0 - 19 y	10	10	13	13	11	17	16	14	7
20 - 59 y	164	176	199	203	237	204	203	196	186
> 60 y	58	71	74	64	74	81	88	98	89
All ages	232	257	286	280	322	302	307	308	282

<b>Accidental poisoning (ICD-9 E850-E858: ICD-10 X40-X44)</b>									
	1993	1994	1995	1996	1997	1998	1999	2000	2001
0 - 19 y	4	5	2	8	5	3	5	7	0
20 - 59 y	41	49	60	38	55	53	42	38	53
> 60 y	9	12	9	13	14	6	9	3	7
All ages	54	66	71	59	74	62	56	48	60

Figure 3: Absolute mortality: suicide and open verdicts (England and Wales)

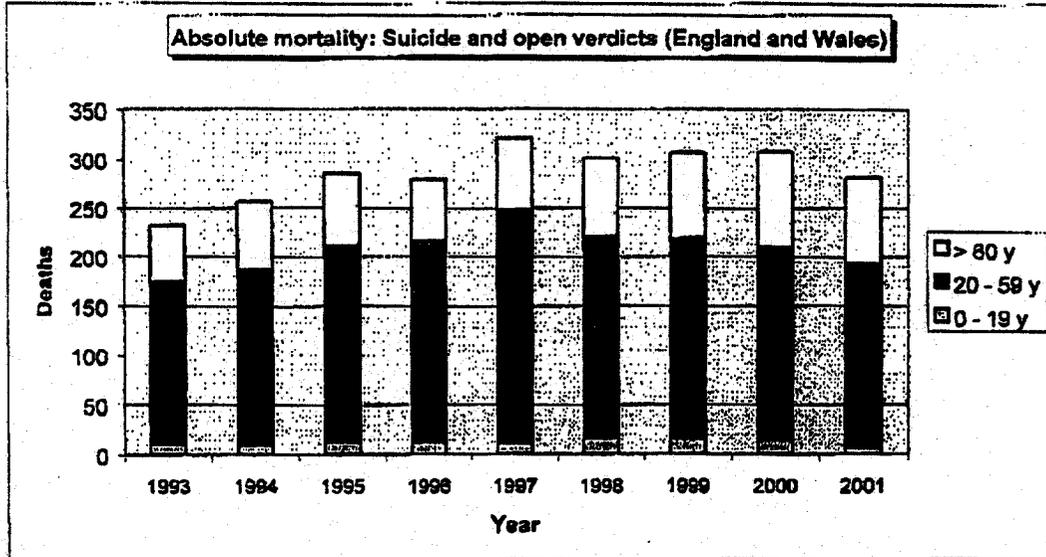
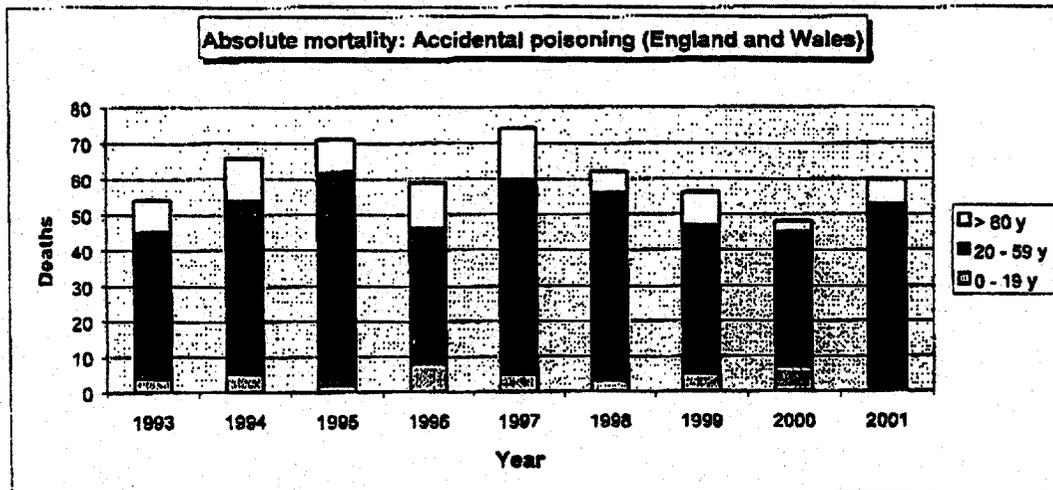


Figure 4: (NB Y axis scale is different as there are far fewer accidental poisonings)



Figures 5 and 6 display the same data corrected for population age distribution (i.e. deaths/million population of each age group). These show that children and adolescents aged <20 years are the age group at lowest risk of fatal co-proxamol overdose and that the burden of highest relative risk has gradually shifted from adults aged 20-59 years to those aged >60. An explanation for the low mortality in the youngest age group (an average of 14 deliberate and accidental deaths/year) is that this is the age group at lowest risk of suicide by any means. Also, co-proxamol is seldom prescribed for this age group although it may be present in the home if prescribed for an older member of the household. It has been shown that young adults aged <25 years who overdose tend to use co-proxamol belonging to a third party rather than their own prescription (Annex 23).

Figure 5:

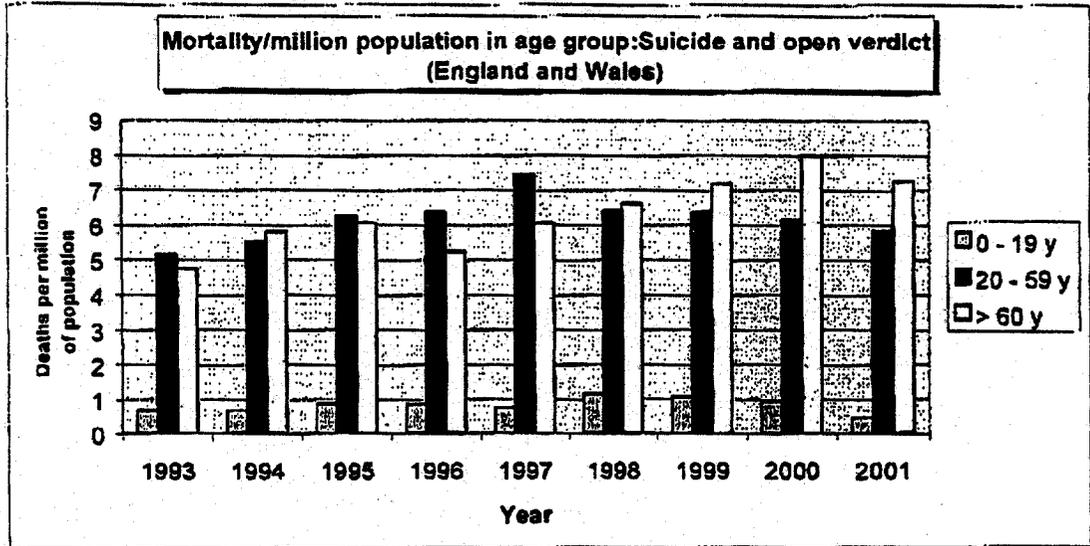
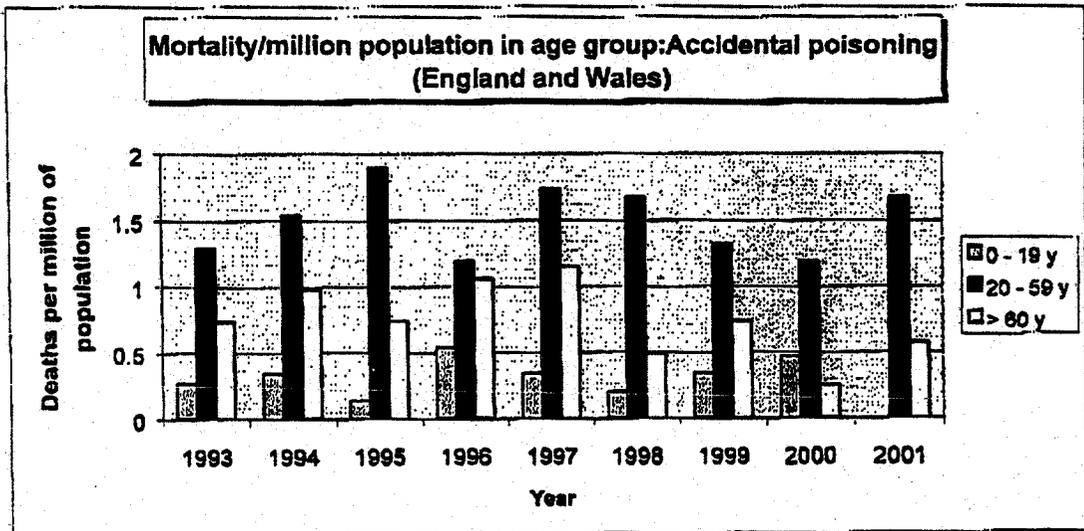


Figure 6: (NB different scale of Y axis)



### 6.2.2 ADROIT adverse drug reaction data

A drug analysis print (DAP) for the period from 1<sup>st</sup> January 1995 to date (Annex 24) contains a total of 96 reports of suspected adverse drug reactions (ADRs), 19 of which had fatal outcomes. Ten ADRs (1 fatal) were reported for the single-constituent product DXP and 139 ADRs (18 fatal) were reported for co-proxamol.

Fourteen of the deaths followed overdose (intentional overdose or overdose 'not otherwise specified').

### 6.2.3 Morbidity data: Hospital data and data from Poisons Units

No hospital admissions data specific to dextropropoxyphene or co-proxamol are available. The Hospital Episodes Statistics data are collected for synthetic opioids in general (ICD 10 code T40.4) but cannot be generated for individual drugs.

### 6.2.4 Enquiries to Poisons Centres

All six Poisons Centres were contacted to request data on enquiries concerning poisonings with DXP-containing products. These take the form of telephone enquiries and interrogations of the TOXBase database. Data received was the number of interrogations of TOXBase for the four countries of the UK. Data regarding telephone enquiries was received from Edinburgh and Newcastle-upon-Tyne. Data regarding case reports was sent by the Belfast Centre.

#### Telephone enquiries

Since the introduction of TOXBase, direct telephone enquiries to the Poisons Centres have decreased overall. The number of telephone enquiries for 1997 to 2003 was obtained from the Edinburgh and Newcastle-upon-Tyne Poison Centres. Figures are as given in Table 3. The number of calls regarding DXP-containing products as a percentage of the total number of calls was of similar magnitude to the national interrogations of TOXBase for each country. The number of telephone calls to the Edinburgh centre were relatively stable with a slight decline towards the end of period as observed for the database enquiries. The number of calls to NPIS Newcastle-upon-Tyne increased to 2000 (both as absolute and relative numbers) and declined thereafter.

Table 3: Telephone enquiries (DXP-products) to NPIS, Edinburgh and Newcastle-upon-Tyne

Year	Edinburgh	Newcastle-upon-Tyne
1997	65 enquiries (1.06% of total)	37 enquiries (1.15% of total)
1998	63 (1.08%)	51 (1.17%)
1999	62 (1.02%)	192 (1.69%)
2000	50 (0.95%)	449 (1.98%)
2001	39 (0.81%)	364 (1.53%)
2002	39 (0.92%)	240 (1.35%)
To Sept 2003	15 (0.55%)	122 (1.24%)

DXP and co-proxamol are no longer included in the Northern Ireland formularies. The Poisons Centre in Belfast sent brief details of case reports of a total of 22 poisonings involving DXP-containing products in the years 1995 – 2002; nearly half the cases involved children in the age-group 1-4 years.

#### TOXbase enquiries

TOXBase enquiries for all drugs have increased steadily from 1999-2002 in absolute terms in Scotland, in England, in Northern Ireland and in Wales but the percentage of queries concerning DXP/co-proxamol have been fairly stable or slightly declining to about 1% of calls in Scotland and England. The relative figure for Wales is slightly lower at 0.66-0.88%, whilst that for Northern Ireland is still lower at 0.3-0.5% of total enquiries, reflecting low usage. (NB It is not possible to determine if accesses to TOXBase were for patients or teaching or if the product entry was viewed several times for the same patient.)

### 6.3 Published Study of drug related suicides in England and Wales

The recently published study by the Centre for Suicide Research at Oxford (Annex 3) found that during 1997-99 co-proxamol alone accounted for 18% of drug-related suicides in England and Wales in individuals aged 10 years and over, compared with 22% with tricyclic anti-depressants alone and 9% with paracetamol alone. The authors found that a higher proportion of suicides in the 10-24 age group (expressed as a percentage of all drug-related suicides in age group) were due to co-proxamol than in the other age groups, as shown in Figures 7 and 8 overleaf.

Figure 7: Drug related suicides and open verdicts (England and Wales) :Male

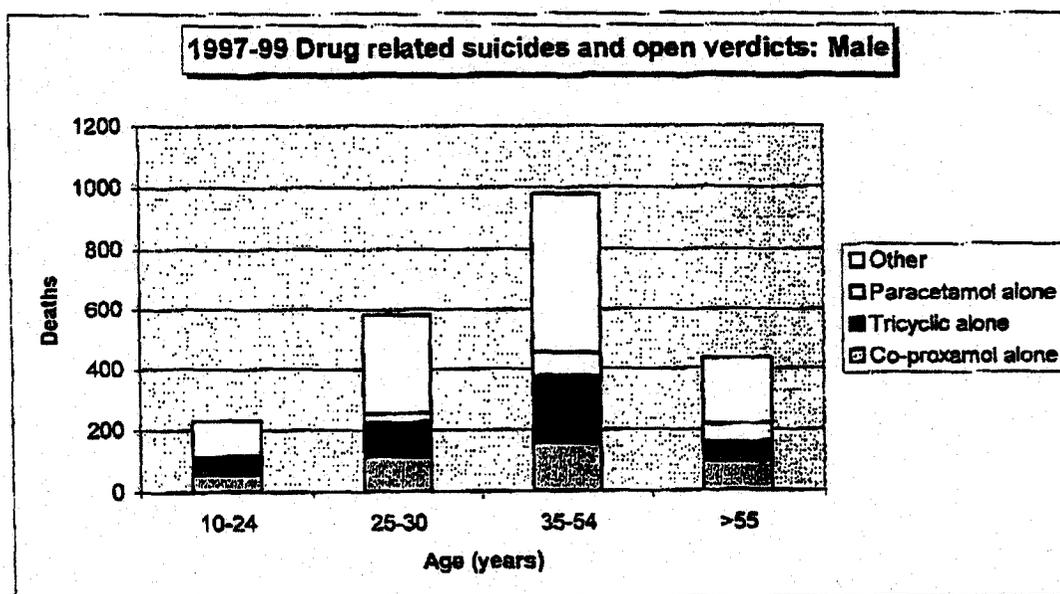
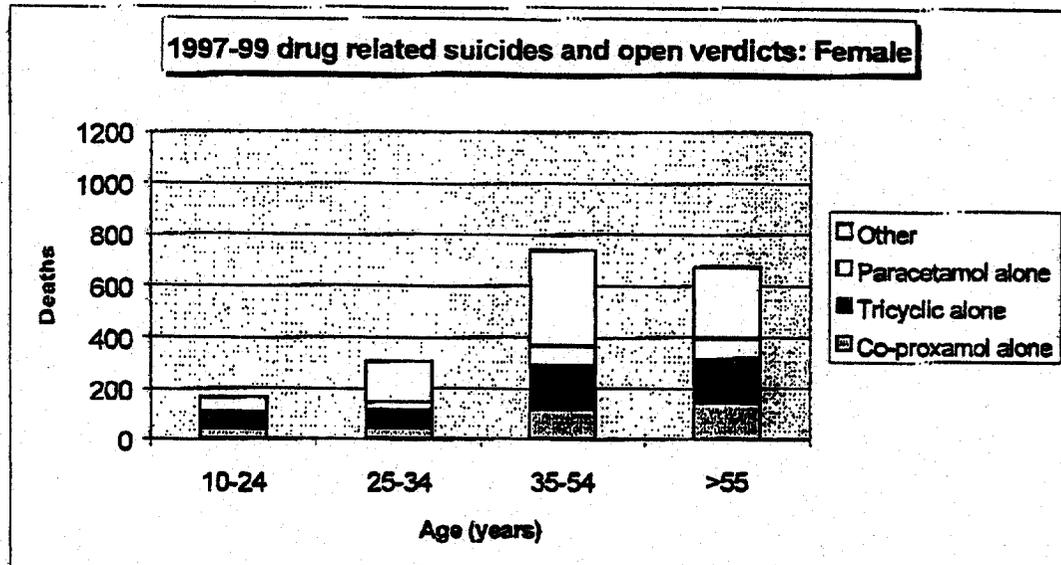


Figure 8: 1997-99 Drug related suicides and open verdicts (England and Wales): Female



**Assessor's comment:**

The drug related suicide rate in 10-24 year olds is lower than for any other age group but compared with other age groups, co-proxamol accounts for a relatively high proportion of this small number of deaths. This may reflect the generally low level of prescribing of any medicines to normally healthy young people. (There is a sex difference; in males the suicide/open verdict rates from tricyclic antidepressants and co-proxamol are identical (23.8% and 22.9% of all drug deaths respectively) but a greater proportion of females overdosed with tricyclics rather than co-proxamol (30.7% vs 25.3%).)

The authors compared the annual rate of drug related suicides and open verdicts in England and Wales with the figures for non-fatal self poisoning in Oxford over the same period in order to calculate an odds ratio for relative lethality. Compared with paracetamol alone, the lethality ratio for co-proxamol was 28.1 (CI =24.9-32.9) and for tricyclics was 12.3 (CI=11.5-13.2).

This calculation of relative lethality may be skewed by local factors such as prescribing patterns for tricyclics and co-proxamol in Oxford, speed of ambulance response and quality of emergency medical care, all of which may impact on the incidence of nonfatal overdose. Nonetheless, the message is clear: paracetamol overdose is a fairly ineffective means of suicide and co-proxamol is twice as likely to be lethal as tricyclic antidepressants.

**Assessor's comment:**

Prescribers are fully aware of the lethality of tricyclic antidepressants in overdose but do not seem to be aware that co-proxamol is much more hazardous.

#### 6.4 Swedish data

Reports concerning the toxicity of DXP including data from the Swedish Poison Information Centre and the National Board of Forensic Medicine were published in the scientific press in the late 1990s onwards. Forensic data published in 2001 indicated that there had been a high number of deaths (~200) annually in Sweden that could be associated with DXP.

**Assessor's comment:**

*Swedish sales data are not available but the DXP market appears to be dominated by single constituent products. There are 7 products containing DXP currently on the Swedish market. Four of these contain DXP napsylate (50 or 100mg) only and the remaining three are compound analgesics, only one of which contains paracetamol.*

## 7 SUCCESSFUL MEASURES TO REDUCE CO-PROXAMOL/DXP PRESCRIBING

### 7.1 UK initiatives

#### 7.1.1 Doncaster

An 1998 audit of suicides in Doncaster during the 4-year period 1995-1998, found that 18 out of 44 (41%) of suicides with prescribed drugs involved co-proxamol. At that time co-proxamol prescribing was 65% higher than the national average. To reduce the amount of co-proxamol in circulation, GPs were asked to be more cautious when prescribing co-proxamol and the Doncaster Royal Infirmary also removed it from their formulary. By August 2003, approximately 60% fewer tablets had been prescribed than in the preceding 4-year period, and only 5 suicides involving co-proxamol had occurred since the beginning of 2000 (Annex 25).

#### 7.1.2 Northern Ireland

The experience of the Belfast Poisons Centre is that since a publicity campaign about sudden death and DXP in the mid 1970s and removal of DXP/ co-proxamol from the N. Ireland formularies, the number of cases of poisoning with DXP-containing products has been low.

#### 7.1.3 Nottingham

At University Hospital in Nottingham, nurse and doctor education has removed inappropriate prescribing of DXP-containing products on post-operative and orthopaedic wards and now it is only given to patients who had used it chronically before admission (Annex 7).

### 7.2 Sweden

Sweden has introduced a series of measures to reduce the incidence of fatal DXP overdose:

#### Seminar

In Spring 1999 the Swedish Medical Products Agency (MPA) with other institutions arranged a seminar on analgesics with the aim of giving a wider perspective on the pharmacology and toxicology of DXP.

#### Website publication

In the same year, a report was published on the MPA web-site discussing inter-individual variations in efficacy, concerns regarding the pharmacokinetics of DXP and its narrow therapeutic index, and the rapid onset of serious symptoms of intoxication in overdose. The dangers of concomitant ingestion with alcohol were also highlighted.

#### Product information

In August 2000 the SPCs of DXP-containing products were updated to include warnings on the risk of overdose, of concomitant ingestion of alcohol (with wash-out periods), the importance of informing the patient of the importance of following the recommended doses and of the risk of concomitant ingestion with alcohol. It was

also advised to prescribe smaller packs and not to prescribe DXP for patients who abuse alcohol or who are suspected of abusing CNS depressants (see informal translation in Annex 25). Similar warnings on overdose and ingestion of alcohol were included in the PIL and labelling (Annex 26). The PIL was also amended to include "NEVER exceed the recommended dose" and "Keep out of the reach and sight of children and adolescents".

#### **Narcotics prescription form**

Since June 2001 prescriptions for DXP-containing products must be written using the special prescription form employed for narcotic containing drugs. This is a security form designed to avoid falsification and is somewhat troublesome to use, hopefully provoking thought about the absolute need for the prescription.

In addition, the MPA recommended the restricted and individualised prescription of DXP and a thorough follow-up of the treatment effectiveness.

Swedish sales of DXP are declining, and the numbers of case reports and inquiries to the Swedish Poisons Information Centre concerning DXP have declined during the period 2000-2003. In the same period fatal DXP the incidence of intoxication has decreased by 62%.

### **7.3 Australia**

The outcome of an initiative restricting co-proxamol prescribing to consultants in a 571-bed teaching hospital was published in 1980 (Annex 21). This restriction greatly reduced hospital pharmacy purchases of both co-proxamol and DXP, especially for inpatients. Overall hospital analgesic usage fell but there were compensatory increases in usage of paracetamol and co-codamol and the usage of co-codamol increased with time.

### **7.4 Norway, Finland and Denmark**

The introduction of strict prescribing rules (1980s) in Norway and Denmark and education of doctors in Finland regarding prescribing (1995) have reduced the numbers of deaths due to DXP (Annex 12).

## **8 OPTIONS FOR ACTION**

### **8.1 Revocation of licence**

The Committee will wish to consider whether, on the basis of current evidence, the risk:benefit evaluation for co-proxamol remains acceptable and will wish to consider whether to recommend revocation of the co-proxamol marketing authorisations.

## **8.2 Restrict indications to chronic osteoarthritis, neuropathic pain and cancer pain**

This is a rational restriction because:

- Studies in acute pain have failed to show efficacy superior to paracetamol alone.
- The pharmacokinetics of dextropropoxyphene do not permit potentially therapeutic blood levels to be reached for several days so, although it might be useful in chronic pain, co-proxamol is not a rational choice of drug for acute use.

Other prescribing restrictions for consideration are:

- **Second line therapy only**

Although there is no robust evidence that co-proxamol has superior analgesic efficacy to full strength paracetamol, it would be rational to restrict the indications for co-proxamol to second-line use only after paracetamol alone has failed.

- **Specialist use only**

A restriction of this nature is technically feasible but would cause major problems for GPs who have many patients on established chronic therapy. An alternative strategy would be to restrict *initiation* of co-proxamol therapy to specialists in order to reduce the accrual of large numbers of new co-proxamol users in the community.

## **8.3 Strengthen warnings in the product information**

All SPCs for co-proxamol and DXP-containing products should contain:

- A contra-indication in patients who are suicidal or addiction-prone
- Warnings concerning the dangers of concomitant ingestion of alcohol and of CNS depressants
- Warnings about the risk of prescribing for patients who are suffering from depressive and other mental disorders.

Key warnings in the PIL should be heavily emphasised:

- NEVER take with alcohol (patients need to know that it really is dangerous, and this is not just a routine general precaution).
- NEVER take more than the recommended dose
- Dispose of any unused medication as soon as possible.

## **8.4 Widen the range of available pack sizes**

The current average monthly prescription is 100 tablets and most licence holders market only a 100-tablet pack (corresponding to 14 days' treatment) but this quantity may exceed the needs of many patients who only use co-proxamol intermittently.

The wider availability of smaller pack sizes should be encouraged in order to prevent retention by the patient of unnecessarily large quantities of co-proxamol. It would also ensure that all patients receive a patient information leaflet on each occasion.

## 8.5 A co-ordinated programme of education and communication

Carefully-timed education and communication is required to alter prescribing behaviours. If prescribers are to adopt measures to reduce their therapeutic dependence on co-proxamol they need to recognise that it is a drug of unproven efficacy that is particularly unforgiving in overdose. They will also need to be given clear guidance on the choice of alternative analgesic drugs. 'Non-prescribing influencers' such as formulary committees, GP prescribing advisers and drug information pharmacists will play a pivotal role in the shift of prescribing behaviour. Whilst some local initiatives have been successful, previous attempts at educating prescribers have failed at a national level because they have been piecemeal activities rather than a concerted campaign using several vehicles simultaneously e.g:

- Focused dialogue with key influencers:
  - Hospital Formulary Committees
  - Royal Colleges (key medical specialties and nursing)
  - RPSGBSeminars or 'consensus meetings' following the Swedish model may have more impact than written communication with these influential individuals as the dialogue would be published by the participants in their professional journals.
- Awareness-raising campaigns in professional media:
  - MHRA website
  - Current Problems in Pharmacovigilance
  - CMO's Update (similar to the recent benzodiazepines warning at Annex 27)
  - Review article in a major medical journal
  - Further strengthening of the BNF warnings
  - Coverage by trade journals

## 9 CONCLUSIONS

On balance, the Committee may consider that the risk:benefit evaluation of co-proxamol is negative for the following reasons:

- The toxicity of co-proxamol in overdose is well established; it is particularly hazardous because death occurs too rapidly for medical rescue. It now accounts for nearly one-fifth of all drug-related suicides in England and Wales.
- Efficacy superior to full dose paracetamol has not been adequately demonstrated for either acute or chronic pain
- Co-proxamol contains submaximal doses of paracetamol and as there is no evidence of synergy with dextropropoxyphene, it does not represent a rational fixed combination product.

However, whilst the efficacy of co-proxamol in chronic pain has not been adequately investigated, it is possible on pharmacokinetic grounds that co-proxamol may only have a full therapeutic effect with chronic dosing. There may therefore be some justification for co-proxamol remaining a therapeutic option for the management of chronic pain.

## **10 ADVICE SOUGHT**

The Committee is asked to consider the risk:benefit evaluation for co-proxamol in the treatment of acute and chronic pain and to advise which measures should be adopted in order to reduce the incidence of self poisoning. In particular,

- 10.1 Revocation of the marketing authorisations for co-proxamol
  - 10.2 Restriction of indications to *chronic osteoarthritis, neuropathic pain and cancer pain*
  - 10.3 Strengthening of product information, especially labels and leaflets
  - 10.4 Encouraging the availability of a wider range of (smaller) pack sizes
- together with:-
- 10.5 An education and communication strategy to change prescribing practice

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**COMMITTEE ON SAFETY OF MEDICINES  
NOT FOR PUBLICATION**

**CSM 2004/16th**

<b>RESTRICTED - COMMERCIAL</b>	<b>PL NUMBER:</b> Several
<b>TITLE OF PAPER:</b> RISK: BENEFIT OF CO-PROXAMOL PRODUCTS	
<b>RISK: BENEFIT ASSESSMENT</b> Responses to public request for evidence on risks and benefits	<b>THERAPEUTIC CLASSIFICATION:</b> Analgesic
<b>LICENCE HOLDER:</b>  Several	<b>PRODUCT NAMES:</b> Co-proxamol Distalgesic Cosalgesic Dolgesic
<b>ACTIVE INGREDIENT:</b> Dextropropoxyphene + paracetamol	<b>PREVIOUS CONSIDERATION BY CSM:</b> 1985 2004/8th
<b>LEGAL STATUS:</b> POM	<b>CONSIDERATION BY OTHER COMMITTEES:</b> SCOP 2004/2nd
<b>SALE/SUPPLY:</b> POM	<b>ASSESSORS:</b>

## **EXECUTIVE SUMMARY**

Following a public request for information on the efficacy and safety of co-proxamol this paper presents:

- A review of the responses to the request for information which provided no new evidence not previously reviewed by CSM.
- Opinion in responses showing that whilst co-proxamol would be missed by some patients and prescribers, no strong case can be made for its continuing availability in a special patient population(s).
- A key point voiced by many respondents was that if co-proxamol were withdrawn, this should be done gradually in order to minimise disruption whilst alternative pain management strategies are established for individual patients.

## **CO-PROXAMOL: RESPONSES TO REQUEST FOR EVIDENCE ON RISKS AND BENEFITS**

### **1 INTRODUCTION**

CSM advice is sought following a public request for information on the efficacy and safety of co-proxamol.

### **2 BACKGROUND**

Co-proxamol is indicated for '*mild to moderate pain*' with a maximum daily dose of 8 tablets. It contains dextropropoxyphene (32.5mg), a weak opioid analgesic that is known to be toxic in overdose and a dose of paracetamol (325mg) that would on its own be considered sub-therapeutic. Co-ingestion of alcohol or other central nervous system depressants significantly increases risk.

Each year 300-400 people in England and Wales die following deliberate or accidental drug overdose involving co-proxamol. Approximately one-fifth of these deaths are considered to be accidental. There is growing concern prompted by recently published UK research showing that co-proxamol alone is involved in almost one-fifth of drug-related suicides and is second only to tricyclic antidepressants as an agent of fatal drug overdose.

The National Institute of Mental Health in England (NIMHE) is an organisation set up by the Department of Health aimed at improving the quality of life for people of all ages who experience mental distress. A key goal of NIMHE's National Suicide Prevention Strategy is to reduce the number of suicides as a result of self-poisoning. Reduction of access to means of suicide, such as by limiting the availability of medicines commonly used in self-poisoning, has been identified by NIMHE as an effective method of achieving this goal.

Dextropropoxyphene was developed in the 1950's and co-proxamol has been marketed since 1965, long before the current system of medicines regulation existed. As a long established medicine, co-proxamol has not been subjected to modern standards of clinical research; clinical trials were often either poorly designed or of very short duration (often just a single dose) and on the whole did not produce definitive results. In particular, there have been no conclusive studies of greater than 48 hours' duration evaluating the effectiveness and safety of co-proxamol in comparison with other medicines (such as paracetamol alone) indicated for mild to moderate pain. For acute pain, co-proxamol, which contains only 325 mg of paracetamol, has not been shown to be more effective than normal strength (500 mg) paracetamol or 325 mg paracetamol alone. Although co-proxamol is mostly used as a long-term treatment for chronic muscular/skeletal pain in the elderly, most of the studies were in relatively young patients treated for acute injuries, obstetric or post-operative pain.

### 3 COMMITTEE CONSIDERATION

CSM first drew prescribers' attention to the proven toxicity of co-proxamol in 1985 and advised a series of precautionary measures to reduce the risk of self-poisoning. In April 2004, the Committee re-evaluated the risk:benefit of co-proxamol products in the light of recent and forthcoming UK publications on fatal co-proxamol overdose, the National Suicide Prevention Strategy and a European Parliamentary question in 2003 on the dangers of co-proxamol.

The Committee advised that it was minded to revoke the marketing authorisations for co-proxamol with a period of consultation seeking to uncover any as yet unidentified group of patients for whom the risk:benefit balance of co-proxamol might be favourable. The Committee was concerned that during this consultation process, available evidence on safety and efficacy should be highlighted to prescribers. The Committee raised the concerns that prescribing advice on alternatives would need to be available and that immediate regulatory action should be avoided.

Following their meeting on 8 July 2004, a CSM Pain Management Working Group have drafted advice on alternative analgesics (published on MHRA website) for CSM consideration. The Working Group did not identify any clinical situations where co-proxamol was of special value.

### 4 REQUEST FOR INFORMATION

The information request *Review of the utility of the pain reliever co-proxamol (Distalgesic; Cosalgesic; Dolgesic) and request for information on risk: benefit* was issued on 30 June 2004 with a deadline for comments of 22 September 2004. It was circulated within the health services, to interested organisations and officials in the Scottish Executive, Welsh Assembly and Northern Ireland (devolved administrations) and published on the MHRA website.

### 5 INFORMATION REQUESTED

Information was sought on the following:

- (i) Any information from clinical trials, observational data or other scientific studies not mentioned in the attached summary, which cast light on the risks and benefits of co-proxamol.
- (ii) Any additional evidence to support the use of co-proxamol in specific patient groups, for whom risk: benefit is favourable – identifying the specific indication, dosage and duration of use.
- (iii) Any evidence of the impact of local restriction or withdrawal of co-proxamol from use, in line with the National Prescribing Centre and

British National Formulary advice, particularly in relation to other analgesics.

Respondents were invited to comment on the suggested options for regulatory action:

- (i) Restricting the indications – for example to a defined use; duration of use (acute or long term); second line therapy where paracetamol alone has failed; and/or specialist initiation of therapy.
- (ii) Further strengthening of warnings in the product information and improvements in label and packaging design with regard to patient safety.
- (iii) Widening the range of available pack sizes – currently most manufacturers provide 100 tablet packs (equivalent to 14 days' treatment) but smaller pack sizes may encourage reduced prescribing and prevent retention by the patient of any unused product.
- (iv) A co-ordinated programme of education and communication for healthcare professionals to alter prescribing behaviours.
- (v) Product withdrawal possibly over a specified timescale.

## 6 INFORMATION RECEIVED

The MHRA has received a total of 52 responses, which can be broadly categorised as follows:

Royal Colleges	7
Replies from specialist pain bodies	3
Pharmacy interest	4
Medical interest	9
Patients	3
NHS	2
Other bodies	6
No comment	8
<b>TOTAL</b>	<b>52</b>

Copies of these responses will be available for perusal by Committee members at the CSM meeting on 13 October 2004.

Key themes covered by the responses are discussed below.

### 6.1 Risk:benefit is generally unfavourable

The majority of respondents did not advocate the widespread use of co-proxamol although the proposed course of action was for many tempered by practical considerations:-

### **6.1.1 Co-proxamol should not remain available**

Organisations responsible for prescribing policy, education and advice unanimously agreed that co-proxamol should not continue to remain available. Comments endorsing withdrawal were received from the British Pharmacological Society, pharmaceutical advisors, primary care trusts and formulary committees, the Royal College of Anaesthetists and a GP and a rheumatologist.

The Royal Pharmaceutical Society of Great Britain was unable to identify any strong reason why co-proxamol should remain generally available but had concerns about the practical aspects of withdrawing it.

### **6.1.2 Co-proxamol should not be initiated in new patients**

The Royal College of General Practitioners (RCGP) did not oppose withdrawal in principle but were concerned about the workload implications for frontline services and suggested the 'option within an option' of allowing chronic users to continue but not allowing any new prescriptions. This approach was also favoured by the Royal College of Physicians and Surgeons of Glasgow.

### **6.1.3 Use of co-proxamol is not endorsed**

The Royal College of Physicians of Edinburgh considered that co-proxamol is unsuitable for widespread general use and recommended a phased withdrawal if 3 years' of restricted use (to patients with chronic pain where paracetamol alone has failed) does not have an impact.

The Royal College of Paediatrics and Child Health does not support the use of co-proxamol in children but feels that it should remain available for other patient groups (e.g. in palliative care).

#### **Assessor's comment:**

*It is difficult for prescribers to reconcile objective knowledge of the risks and benefits of co-proxamol with the realities of managing their existing patients. Although the compromise solution of stopping initiations whilst allowing chronic users to continue with co-proxamol appears rational, it is unlikely to have the desired effect. A major proportion of co-proxamol usage is long term so even if there are no new initiations, it will continue to be present in many households for years to come. Also, it is almost inevitable that many prescribers will be uncommitted to change and if co-proxamol remains available for chronic use, they will continue to initiate it in new patients.*

### **6.2 Special patient groups for whom risk: benefit may be positive**

Some clinicians, mainly rheumatologists, palliative care specialists, 3 GPs and a surgeon together with the Royal College of Physicians of Edinburgh, The British Pain Society and patient/carer organisations identified special patient groups in whom co-proxamol may have a special place:-

- Patients in whom NSAIDs were contraindicated/not tolerated/ineffective

- Patients who cannot metabolise codeine to morphine as a result of unfavourable CYP 2D6 polymorphism.
- Patients who cannot tolerate codeine due to nausea and constipation. This group was also identified by one doctor, the BMA GPs' Committee and three individual patients responding to the MHRA request for information.

**Assessor's comment:**

*All of these comments were based on the unproven assumption that co-proxamol has superior efficacy to paracetamol 1g alone.*

*Whilst some respondents suggested that there may be some patients for whom co-proxamol does indeed provide something not offered by other analgesics, most, but not all ignored the possibility that patients may feel better on co-proxamol due to its non-analgesic side effects. If required, these adjunctive effects could more appropriately be achieved by prescription of the necessary sedative, anxiolytic or antidepressant.*

- The Pain Relief Foundation's Pain Research Institute discussed research in patients in whom the efficacy of strong opioids is reduced due to hyperalgesia, allodynia and/or opiate tolerance. It was suggested that dextropropoxyphene may have a unique mechanism of analgesic action via N-Methyl D-Aspartate (NMDA) receptor antagonism and amine (noradrenaline and serotonin) re-uptake inhibitory activity. On this rationale, one palliative care physician is using dextropropoxyphene as part of a methadone regimen in patients who have developed resistance to other strong opioids.

**Assessor's comment:**

*Published data (Neuroscience Letters 2000; 295; 21-24) on the effects of dextropropoxyphene and other opioids on N-Methyl D-Aspartate (NMDA) receptor antagonism in rats are presented in the context of possible clinical implications for the treatment of neuropathic pain. However, the postulated role of dextropropoxyphene in this type of pain is not unique there are already well established treatment options for neuropathic pain such as valproate, carbamazepine and tricyclic antidepressants.*

### **6.3 Local initiatives to reduce GP prescribing have proved only partially successful**

Whilst hospital formulary committees can directly control co-proxamol usage in secondary care, reductions in GPs' prescribing can only be achieved by winning their personal commitment to change long-established clinical practice. This is clearly very difficult as education and financial incentives to reduce prescribing are in direct conflict with the perceived needs of individual patients, each of whom is (at least for the duration of consultation with their GP) a special case. Details were provided of interventions that had met with some success but none was able to largely eliminate GP usage of co-proxamol.

**Assessor's comment:**

*Local 'hearts and minds' initiatives or local formulary restrictions described by respondents achieved only 20-30% reductions in GP prescribing. Although this is a significant achievement, it is obviously insufficient to control the risks of fatal co-proxamol overdose. Furthermore, a national educational programme may not achieve as much 'buy in' from GPs as local initiatives.*

Some respondents, including the RCGP and the Association for Nurse Prescribing (co-proxamol is not included in the Extended Formulary but they would like to have it for second-line use) felt that prescriber education was an important strategy for preventing co-proxamol fatalities. As discussed, past experience has shown that this measure would be only partially successful.

### **6.4 Logistical implications of ceasing availability of co-proxamol**

A recurring concern amongst respondents, regardless of whether they considered that co-proxamol might be of value, was that transferring established co-proxamol users to other therapies would involve a huge burden of additional work for hard-pressed frontline services. It was acknowledged that if GPs were given sufficient notice, much of the switch could be achieved during routine medication reviews although many patients would require additional consultations in order to establish the optimal alternative medication.

**Assessor's comment:**

*Elderly chronic pain sufferers tend to continue on the same treatment for many years whilst their health and mobility gradually decline. GPs and their patients should be encouraged to see the co-proxamol withdrawal exercise as an opportunity to take stock by reviewing pain control and assessing the need for antidepressants and other adjuvant drugs, physiotherapy, occupational therapy, social care and other forms of assistance.*

### **6.5 Erroneous perception of risk**

The British Society for Rheumatology considered that osteoarthritis patients are older and statistically at less risk of committing suicide than the young so the problem is that co-proxamol is getting into the wrong hands rather than

inappropriate prescribing. However, Office of National Statistics epidemiological data show that after correcting for age group population size, the risk of fatal co-proxamol self-poisoning is highest in patients aged >60 years.

The RCGP suggested that the high incidence of suicide with co-proxamol merely reflected its widespread use. CSM has previously noted evidence that co-proxamol has a narrow safety margin and is particularly hazardous in overdose compared with other agents.

#### **6.6 Alternative analgesics may not be safer**

Several respondents considered that the efficacy and suicide potential of other combination analgesics has not been adequately evaluated (Faculty of Pharmaceutical Medicine, RCGP, Association for Nurse Prescribing and others). They suggested that if co-proxamol were unavailable, there would be an increase in use of other agents which may be no safer in overdose so that overall the numbers of suicides and accidental self-poisonings may not be reduced. Another concern was the abuse potential of codeine products although RCGP recognised that this was also a problem for co-proxamol.

**Assessor's comment:**

*There is evidence that dextropropoxyphene-containing products are intrinsically more hazardous in overdose due to the swift onset of respiratory depression and dextropropoxyphene-specific cardiotoxicity, its low therapeutic ratio and the potential for interaction with alcohol. Therefore the substitution of other less toxic medicines for mild-moderate pain is likely to result in a smaller overall number of suicides and accidental fatal self-poisonings.*

#### **6.7 Research data on co-proxamol overdose**

Concern regarding toxicity was voiced by respondents describing their local research on co-proxamol fatalities.

#### **6.8 Pack size restriction**

There was little support for this option, especially from RCGP, as most co-proxamol usage is chronic repeat prescribing.

**Assessor's comment:**

*Most repeat prescriptions are for at least 1 month's supply of medication. It is possible that those respondents who did support pack size restrictions were unaware that as little as 3 day's supply of co-proxamol (24 tablets) is more than enough for a fatal overdose.*

## **7 DISCUSSION OF RESPONSES TO REQUEST FOR INFORMATION**

No objective new information was provided concerning the risk:benefit of co-proxamol. Opinion was broadly divided between evidence-based prescribing advisers and front line clinicians, mainly GPs, rheumatologists and pain or palliative care specialists (who did not always realise that their patients were an at-risk population) together with patients currently using co-proxamol. As might be expected, prescribing advisers (including the Royal College of General Practitioners) were unanimously in favour of withdrawing co-proxamol, whilst current prescribers and patients tended to favour its continued availability.

The option of allowing chronic users to continue receiving co-proxamol whilst ceasing initiations was proposed as an alternative to withdrawal. (This strategy should also preclude the reissue of co-proxamol to lapsed users.)

Where respondents have discussed withdrawal of co-proxamol, the need for a planned and prolonged withdrawal process has been emphasised. If the withdrawal is managed well, patients will see it as a positive move, prompting a review of their medication and introduction of more appropriate forms of treatment and support.

## **8 CONCLUSIONS ON PUBLIC REQUEST FOR INFORMATION**

No further scientific evidence was provided via the public/healthcare professional request for information to support a favourable risk:benefit. The case made in support of the continued availability of co-proxamol is based on clinical practice.

There was limited enthusiasm for reduced pack size or educational programmes as safety measures.

If co-proxamol were to be withdrawn, the process should be sufficiently gradual to avoid significant disruption to frontline health services.

## 9 OVERALL DISCUSSION

There is no evidence that co-proxamol is an analgesic step up from paracetamol and patient preference is probably due to the adjuvant CNS effects of the opioid component, hence the liability to abuse and dependence. If these effects are required in an individual patients appropriate adjuvant drugs (e.g. hypnotic, anxiolytic or antidepressant) should be prescribed together with full strength paracetamol.

The role of co-proxamol in chronic use is less clear due to concerns about the acceptability of alternative analgesics but as the popular view that co-proxamol is 'stronger' than paracetamol alone is not evidenced-based, it is inappropriate to regard co-proxamol as a *second line* agent in chronic pain. Based on analgesic efficacy, the obvious alternative to co-proxamol is full strength paracetamol.

Past experience has shown that local educational initiatives alone do not have a major effect on prescribing behaviour and it is unlikely that any changes to the product information (namely restricted indications) will significantly reduce usage while co-proxamol remains freely available.

Where respondents have discussed withdrawal of co-proxamol, the need for a planned and prolonged withdrawal process has been emphasised. If managed well, patients would see the withdrawal process as a positive move, prompting a review of their medication and introduction of more appropriate forms of treatment and support. Under these circumstances, optimised product information and education would be of vital importance.

## 10 OVERALL CONCLUSION

No further scientific evidence was provided via the public/healthcare professional request for information to support a favourable risk:benefit. The case made in support of the continued availability of co-proxamol is based on clinical practice, mostly by GPs, rheumatologists and palliative care or pain specialists.

The Committee will wish to consider whether if co-proxamol is not withdrawn completely it is likely to continue to be extensively used, and whether withdrawal in a planned manner over a period of time is a preferred option.

**Response to Propoxyphene Citizen Petition**  
**Project List**

<b>Task</b>	<b>Responsible Attorney</b>	<b>Status</b>
Obtain all materials and data cited in the CP	Library	In Progress
Search medical literature for information related to propoxyphene	SB	In Progress
Obtain all publicly available documents regarding the UK withdrawal	SB, JB (London)	In Progress
Obtain documents filed in connection with 1978 Citizen Petition seeking withdrawal of propoxyphene drug products	SB	In Progress
Obtain adverse event reports related to propoxyphene drug products	SB	In Progress
Review NDA		
Review IMS data regarding propoxyphene drug use and prescription trends		
Identification of all countries that have propoxyphene drugs on the market and the amount of use	JT	In Progress
Obtain public comments and documents that support availability of propoxyphene drugs and their use in pain management	SB	In Progress
Identify physician that can attest to propoxyphene's importance in treatment "arsenal"	SB	In Progress
Examine success rate of petitions filed by Public Citizen for other drug products	SB	In Progress
Outline response to CP	DB/CH	In Progress
Identify and solicit pain management advocacy and other patient support groups	SB	In Progress
Research applicability of Swedish data to US	SB	
Research appropriateness of using DAWN data for determining drug safety.	SB	In Progress.