

General Dental Council
 General Dental Practitioners Association
 General Medical Council
 General Optical Council
 General Practitioners Association (NI)
 General Practitioners Committee
 General Practitioners Committee (Wales)
 Genetic Interest Group
 GlaxoSmithKline
 Guild of Healthcare Pharmacists
 HCSA
 Health Development Agency
 Health Food Manufacturer's Association
 Health Professions Council
 Health Promotion England
 Health Protection Agency
 Health & Safety Executive
 Health Service Commissioner
 Health Which?
 Help the Aged
 HFMA
 Hoechst Marion Roussel
 Home Office
 Human Genetics Commission
 Icon Regulatory Division
 IDRAC SAS
 IFA
 IHRC
 Imperial Cancer Research Fund
 Independent Healthcare Association
 Institute of Biology
 Insulin-Dependent Diabetics Trust
 Internal Holistic Aromatherapy
 International Research Consultants
 International Society for Pharmaco-epidemiology (ISPE)
 Joint Committee on Vaccination and Immunisation (JCVI)
 Joint Consultants Committee
 Joint Royal College of Ambulance Service
 Kings College Hospital
 Leukaemia Care
 Life
 Local Authority Central Office of Trading Standards (LACOTS)
 London School of Hygiene & Tropical Medicine
 Long-Term Medical Conditions Alliance
 Lorex Synthelabo UK & Ireland Ltd
 Lymphoma Association
 Macmillan Cancer Charity
 Medicines Commission
 Medical Defence Union
 Medical & Dental Defence Union of Scotland
 Medical Monitoring Unit (MEMO) University of Dundee

Medical Protection Society Ltd
 Medical Research Council
 Medical Toxicology Unit
 Medical Women's Federation
 Menarini Pharmaceuticals UK Ltd
 MIND
 Ministry of Defence
 MIMMS (Haymarket Medical Publishing Ltd)
 National AIDS Trust
 National Assembly for Wales, Health Department
 National Association of GP Co-operatives
 National Association of Women Pharmacists
 National Association of Private Ambulance Service
 National Asthma Campaign
 National Back Pain Association
 National Board for Nursing, Midwifery & Health Visiting (NI)
 National Care Standards Committee
 National Consumer Council
 National Council of Women of GB
 National Council for Hospices and Specialist Palliative Care Services
 National Eczema Society
 National Federation of Women's Institutes
 National HIV Nurses' Association (UK)
 National Institute for Clinical Excellence
 National Institute for Mental Health England
 National Osteoporosis Society
 National Meningitis Trust
 National Pharmaceutical Association
 National Patient Safety Agency
 NCH & SPCS
 Neonatal and Paediatric Pharmacists Group
 Neurological Alliance
 NHS Alliance
 NHS Confederation
 NHS Direct
 NHS Information Authority (Coding & Classification)
 NHS Pharmaceutical Quality Control Committee
 NMMA
 Northern Ireland Ambulance Service
 Northern Ireland Consumer Council
 Novartis Consumer Health
 Novartis Horsham Research Centre
 Nursing & Midwifery Council
 Ophthalmic Group Committee
 Orphan Europe (UK) Ltd
 Pain Concern
 Pain Relief Foundation
 Paediatric Chief Pharmacists Group
 Paramedics Board
 Patients Association
 Peninsula Medical School

Pharmaceutical Contractors Committee (Northern Ireland)
 Pharmaceutical Journal
 Pharmaceutical Quality Group
 Pharmaceutical Services Negotiating Committee
 Pharmaceutical Society for Northern Ireland
 Pharmacy Insurance Agency
 Pfizer Consumer Healthcare
 Pfizer Ltd
 Pharmacia Ltd
 PharMag
 PI Pharma
 Primary Care Pharmacists Association
 Proprietary Association of Great Britain
 Prostate Cancer Charity
 Public Health Laboratory Service Board
 Quality Improvement Scotland (NHS)
 Reckitt Benckiser
 Registered Nursing Home Association
 RETHINK
 Royal College of Anaesthetists
 Royal College of General Practitioners
 Royal College of General Practitioners (NI)
 Royal College of Midwives (London)
 Royal College of Midwives (NI)
 Royal College of Midwives (Scotland)
 Royal College of Nursing
 Royal College of Nursing (Northern Ireland)
 Royal College of Nursing (Wales)
 Royal College of Nursing (Scotland)
 Royal College of Obstetricians & Gynaecologists
 Royal College of Ophthalmologists
 Royal College of Paediatrics and Child Health
 Royal College of Pathologists
 Royal College of Physicians & Surgeons (Glasgow)
 Royal College of Physicians (Edinburgh)
 Royal College of Physicians (London)
 Royal College of Psychiatrists
 Royal College of Radiologists
 Royal College of Surgeons (Edinburgh)
 Royal College of Surgeons (England)
 Royal College of Surgeons (Faculty of Dental Surgery)
 Royal Colleges of Physicians: Faculty of Pharmaceutical Medicine
 Royal Colleges of Physicians: Faculty of Public Health
 Royal Pharmaceutical Society of Great Britain
 Royal Pharmaceutical Society of Great Britain (Wales)
 Royal Pharmaceutical Society of Great Britain (Scotland)
 Royal Pharmaceutical Society of Great Britain (Welsh Executive)
 Royal Society of Chemistry
 Royal Society for the Promotion of Health
 SANE

Safety in Health and Social Care Group (SHSCG) (Northern Ireland)
 Sangstat UK Ltd
 Scottish Ambulance Services
 Scottish Association of Health Councils
 Scottish Biomedical Association
 Scottish Consumer Council
 Scottish Deans Medical Curriculum Group
 Scottish General Practitioners committee
 Scottish Executive, Department of Health
 Scottish General Medical Services Committee
 Scottish Medical & Dental Protection Society
 Scottish Pharmaceutical Federation
 Scottish Pharmaceutical General Council
 School of Pharmacy, Queen's University, Belfast
 Scottish Specialists in Pharmaceutical Public Health
 Scrip Ltd
 Social Audit Unit
 Skin Care Campaign
 Small Business Service
 Social Audit
 Society of Pharmaceutical Medicine
 Society of Radiographers
 St Andrew's Ambulance
 St John Ambulance
 St John Ambulance (NI)
 Sub-Committee on Pharmacovigilance (SCOP)
 TAPASI
 Terrance Higgins Trust
 The British Thoracic Society
 The Council of Heads of Medical Schools
 The Lancet
 The Society of Chiropractors & Podiatrists
 The UK Inter-Professional Group
 Third Sector
 TIC-TAC Administration
 Tutsells Enterprise IG (The Brand Union Limited)
 UK Agricultural Supply Trade Association
 UK Breast Cancer Coalition
 UK Clinical Pharmacy Association
 UK Drug Utilisation Research Group (UK-DURG)
 UK Gout Society
 UK Homoeopathic Medical Association
 UK Inter-Professional Group
 Ulster chemist Review
 Unified Register of Herbal Practitioners
 University of Aberdeen: Department of General Practice & Primary Care
 University of Nottingham: Division of Primary Care
 University of Keele: Primary Care Sciences Research Centre
 University of Southampton: Division of Primary Care
 URIACH & CIE SA
 Veterinary Medicines Directorate (VMD)

Viartis Pharmaceuticals Ltd
Volunteer Development Scotland
Welsh Consumer Council
Welsh National board for Nursing, Midwifery & Health Visiting
Women in Medicine
Women's National Commission

Annex 5

**OUTCOME OF THE REVIEW OF THE UTILITY OF THE PAIN RELIEVER
CO-PROXAMOL AND THE REQUEST FOR EVIDENCE ON THE RISKS
AND BENEFITS**

Number	Organisation	Page number
1	The Pain Relief Foundation's Pain Research Institute	8
2	A GP	9
3	Doctor in the Navy	9
4	Consultant in the Navy	10
5	Consultant Rheumatologist	10
6	Royal college of Physicians	3
7	Generics UK*	NA
8	Welsh Consumer Council*	NA
9	Patient	12
10	Solihull PCT	13
11	North Cumbria Medicines Management Group	13
12	Compton Hospice	13
13	Northumberland Care Trust	14
14	North Tees PCT	14
15	BCDS*	NA
16	NIPEC*	NA
17	Scottish Consumer Council**	NA
18	National Association of Private Ambulance Services	17
19	Trent Medicines Information Service	7
20	Patient	12
21	Patient	13
22	Consultant psychiatrist	10
23	GP	10
24	British Pharmacological Society	8
25	Royal College of Ophthalmologists*	NA
26	GP	10
27	Sandwell and West Birmingham Hospitals NHS Trust Forensic Toxicology Section	14
28	Association of Chief Police Officers in Scotland	17
29	Community Health Division of NHS Ayrshire and Arran	14
30	A Pharmaceutical adviser from South and East Dorset Primary Care Trust	14
31	Scottish Specialists in Pharmaceutical Public Health Group	8
32	A Pharmaceutical Adviser from the Bedfordshire Heartlands PCT	15
33	The GP Committee of the British Medical Association	11
34	The British Pain Society	8
35	Association for Nurse Prescribing	16
36	The Society of Radiographers*	NA
37	The National Pharmaceutical Association*	NA
38	The North West London Hospitals Arthritis Centre	11
39	Oncologists and Rheumatologists at the Sheffield Teaching Hospitals NHS Trust	15

Number	Organisation	Page number
40	The National Council of Women of Great Britain	18
41	The Royal College of Anaesthetists	3
42	Royal College of General Practitioners	4
43	Royal College of Physicians of Edinburgh	5
44	Pain Concern	9
45	Arthritis Care	16
46	British Society for Rheumatology	17
47	Royal College of Physicians and Surgeons of Glasgow	5
48	Royal College of Paediatrics and Child Health	6
49	Faculty of Pharmaceutical Medicine of the Royal College of Physicians	6
50	County Durham and Darlington Priority Services NHS Trust	16
51	The Royal Pharmaceutical Society of Great Britain	7
52	Tayside Drug and Therapeutics Committee	16

A letter 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). A copy of the letter appeared on the MHRA's website. The MHRA has received a total of 52 responses, which can be broadly categorised as follows:

Royal Colleges	7
Pharmacy interest	4
Replies from specialist pain bodies	3
Medical interest	9
Patients	3
NHS	12
Other bodies	6
No comment	8
TOTAL	52

A summary of the main issues raised in each response is set out below.

REPLIES FROM THE ROYAL COLLEGES

The **Royal College of Physicians** stated that they wished to draw attention to an article that might be of interest. This was an analysis of admissions to hospital with deliberate self-harm (DSH) using Hospital Episode Statistics (HES). [Admissions to hospital with deliberate self-harm in England 1995-2000: an analysis of Hospital Episode Statistics. Wilkinson S, Taylor G, Templeton L, Mistral W, Salter E, Bennett P. *Journal of Public Health Medicine* 2002;24:179-183]. This was the first published analysis of the national picture of DSH, and using HES means that it was possible to cover large numbers. For example, paracetamol, as the primary means of self-poisoning, reached a maximum in 30,918 admissions in 1997/98, and fell to 26,096 in 1999/00, an 18.4% decrease. Paracetamol as a secondary agent in admissions rose from 5,133 in 1995/96 to 8,385 in 1999/00, a 63.3% increase. This study gave the whole national picture on paracetamol for DSH as a background. One of the authors indicated that he would be happy to see if their database could be further analysed to produce data specifically on dextropropoxyphene if the MHRA would find it helpful. They noted that in the 'Next Steps' section of the Agency's document the possible reduction in available pack sizes of Co-proxamol was referred to. They felt this might be justified as they believed that one reason for the reduction in episodes of deliberate self-harm with paracetamol identified in the above study might have been the introduction of smaller pack sizes of this drug. (6)

The **Royal College of Anaesthetists** stated that a combination of dextropropoxyphene and paracetamol offered no greater pain relief in the hospital environment than a codeine and paracetamol combination. Additionally, the toxicity of the Co-proxamol preparation was highlighted as a particular concern. The overall opinion of the senior anaesthetists representing the College was that Co-proxamol would not be missed from the array of analgesics currently available for hospital analgesia. (41)

The **Royal College of General Practitioners** stated that they welcomed the MHRA's concern about the potential adverse effects and the abuse potential of Co-proxamol, but strongly urged the MHRA not to consider Co-proxamol in isolation but instead to consider a broader approach to effective and safe use of analgesics overall. It would be unhelpful, for example, if the drug was withdrawn, or its use limited, if alternatives were not proposed. The high frequency of the involvement of Co-proxamol in fatal overdose might partly reflect its wide usage and availability, rather than just its potential for harm. Co-proxamol was prescribed widely where simple analgesics were ineffective and opioids were deemed inappropriate. Therefore a considerable population of users would have severe chronic pain, in itself linked to increased frequency of suicide. Therefore the user group might be particularly high risk for suicide. Most Co-proxamol was used for courses significantly longer than 48 hours, and many patients used the drug for months or years. Many recipients were elderly. They stated that the Pain Society were very keen to press for NICE guidance on the treatment of persistent relief in primary care and this review could link to any activity in that arena. Co-proxamol might be misused and there was anecdotal evidence of some degree of bartering or selling of the drug on the street, usually informally between friends rather than by organised crime or drug suppliers. They questioned what medications could be used to substitute for Co-proxamol; was there any creditable evidence they would have a reduced propensity for harm, involvement in fatal overdose, or abuse / misuse? They were not aware of any other studies or information that was not mentioned except that they would draw attention to the British National Formulary and the National Prescribing Centre (MeReC Bulletin Volume 11, November 2000) where the poor efficacy of Co-proxamol had been highlighted. They were not aware of any other evidence that supported the use of Co-proxamol, apart from the very anecdotal one that some patients certainly seem to like it for pain relief. This evidence came from their members as practising GPs, where there could often be difficult negotiations between patients and members as they tried to wean patients off Co-proxamol. It was also backed by a recent (as yet unpublished) study in one practice in Grampian, in which a look was taken at the use of analgesics by people who had chronic pain. In this practice Co-proxamol was the most frequently prescribed analgesic. Given the preparation's popularity, it would be important that any studies looking at the safety considered usage rates. Like all combination analgesics, the evidence base of risks and benefits of Co-proxamol was very weak and it might be highly inappropriate to focus only on Co-proxamol without further assessments of other combination pain-relieving drugs. There was likely to be considerable impact on practices and patients, if such a highly prescribed drug were restricted or withdrawn. This was not to say that either action should not be done, but rather that any actions would need to be very carefully thought through. The impact of withdrawal could also be observed from the Northern Ireland experience. They considered that restricting the indications, particularly if reinforced by a widespread and prolonged campaign of prescriber and patient education, and a carefully considered range of options might have some impact. They stated that further strengthening of warnings in the product information and improvements in label and packaging design with regard to patient safety was reasonable but could have a perverse result: by alerting patients to the fatal potential of such drugs. They were not convinced that offering a wider range of smaller pack sizes (less than 100 tablets) would decrease prescribing as most prescriptions were of 1 month's duration or longer, often as a repeat prescription. The workload implications and effect on the

front line service of severe withdrawal or limitation of Co-proxamol would be considerable. They asked if there was any evidence that transferring patients to other codeine containing compound analgesics would result in a decrease in the overall number of suicides. An option within this option of withdrawing the drug might be to allow chronic users of Co-proxamol to continue to take the drug (with appropriate warnings), but not allow new prescriptions. (42)

The **Royal College of Physicians of Edinburgh** stated that there was no published or unpublished evidence to suggest that Co-proxamol was better than paracetamol in the treatment of acute pain whether post operative or not. With regards to the management of chronic pain, to their knowledge there were no well-conducted studies that assessed the efficacy of Co-proxamol. However there was opinion of some of those who worked in pain clinics, that patients who suffered with chronic pain had a preference for Co-proxamol over paracetamol and over other prescription only containing paracetamol mixtures because it was less constipating. As regards overdose of Co-proxamol with or without alcohol, the evidence was clear. Co-proxamol alone or in combination with alcohol was the cause of substantial morbidity and mortality each year in the UK and clinical experience suggested that the majority of those who ingested this combination had been prescribed Co-proxamol for acute pain. It was the experience of UK National Poisons Information Service Center Directors that there was a high incidence of sudden death with dextropropoxyphene since its introduction in the 1960's. Thus, the College believed the use of Co-proxamol should be limited to the treatment of chronic pain where paracetamol alone had failed. It would require a coordinated programme of education and communication for Health Care Professionals to alter prescribing behavior. Although it would seem reasonable to recommend that appropriate chronic studies on efficacy were performed, the generic manufacturers would clearly not be in a position to undertake such studies. They stated that unless the restrictions recommended above had an impact, it would be appropriate in three years to consider a phased withdrawal of the product, as the respiratory and cardiotoxicity of this product made it unsuitable for widespread general use. (43)

The **Royal College of Physicians and Surgeons of Glasgow** noted the concerns about the number of fatalities due to Co-proxamol self-poisoning and also acknowledged that the evidence base supporting a specific role for Co-proxamol was weak. It was however mindful of the fact that Co-proxamol was a very widely used analgesic, their local estimates in Scotland suggested that up to 100,000 individuals might take Co-proxamol at sometime during a calendar year. Indeed its usage was substantially greater than that for tricyclic antidepressants which, in fact, lead to an even greater number of fatalities although there does not seem to be any proposal to further restrict their availability. The College was also concerned about the principle involved in regulating a medicine not based on its safety and efficacy in appropriate usage but on its safety in overdose. They stated that this represented a new move for the Licensing Authority and one which should not be taken lightly as there was a potential for many other pharmaceuticals to be perfectly safe and effective when used appropriately but be less safe than alternatives in overdose. The wide usage would imply that prescribers and patients believed that it had a significant role. Certainly it provided an alternative in a part of the Pharmacopoeia which was relatively short of options. The College also noted that the very widespread usage in primary care would make total withdrawal of the drug a difficult problem to manage, with large

numbers of patients having to be switched to alternative therapies. The College took the view that an incremental approach should be adopted. At the present time, Co-proxamol should not be advised for short-term use (where there are appropriate alternatives) and should be avoided in patients with a potential for misuse including known or suspected drug addicts, patients with known or suspected alcohol problems and patients with psychiatric problems or a history of self harm. New long-term prescribing should also be actively discouraged in both primary and secondary care but efforts to induce a wholesale switch of prescribing in a large number of chronic Co-proxamol users would not be a sensible use of health service resource. A more gradual approach with advice about appropriate alternatives, coupled with recognition that there might be patients for whom Co-proxamol provided something not offered by other analgesics would seem more sensible. It should be recognised that there might be particular patient groups, for example the terminally ill or patients with gastrointestinal problems, where Co-proxamol might in fact offer specific benefits. The College did not believe that specialist initiation of therapy would be appropriate, and given their belief that short-term use was not appropriate making available smaller packs did not seem sensible. Finally, the College wondered whether the issue of safety in overdose was to be more widely applied as a criterion for drug regulation. It would appear that agents such as tricyclic antidepressants and mefenamic acid might be seen as other areas where equally effective safer alternatives existed. (47)

The Royal College of Paediatrics and Child Health stated that dextropropoxyphene was infrequently used in children. It was not included in "Medicines for Children" because there was no positive literature evidence of benefit compared to paracetamol alone and there had been no call for its inclusion on the basis of need and use by practitioners. They were aware, however, that it was used in some pain clinics and palliative care to a small extent. Young people would be expected to be as susceptible to fatality in overdose as adults are although they had been unable to find any data on the prevalence of its use in this way in young teenagers and younger individuals. They would support steps 1-4 under next steps in the discussion paper but given its use in palliative care and pain clinics would be unable to support complete withdrawal. It would be possible to support measures to reduce risk in general by restricting indications and providing education programmes via the RCPCH and NPPG and by its status in "Medicines for Children" and the BNF for Children. (48)

The Faculty of Pharmaceutical Medicine of the Royal College of Physicians stated that there might be arguments in favour of restricting the availability of Co-proxamol by limiting pack size etc and they would encourage an education programme for both physicians and patients. They did not believe that the paper produced made the case for more severe regulatory action and stated that it should take into account wider issues surrounding pain management and deliberate self-harm. They would be very concerned if the data from the ONS were taken at face value, as the data might be very inaccurate without checking whether forensic toxicology backed up what was stated on the death certificate. Dextropropoxyphene was one of a number of opioids used in combination with paracetamol for the treatment of mild to moderate pain. The other most commonly used ones were codeine and dihydrocodeine, which were also available in low dose as OTC products. Before any action was taken on Co-proxamol they recommended a review of the efficacy and overdose potential of these agents as it might be that the evidence for these products was no better in terms of efficacy than it was for Co-proxamol. In addition there was the possibility that the

number of suicides and accidental self poisoning would not change, there would simply be a change in the agents used. Analgesic studies, whether for acute pain or chronic pain were notoriously erratic in their results and often showed a surprising placebo response. They also pointed out that there was growing concern about the misuse potential of codeine and dihydrocodeine, even within the OTC products. They also noted that the tricyclic antidepressants, especially amitriptyline, were now used extensively in pain management and the wider availability of this product for this indication might increase the risk of suicide attempts and accidental overdose. Finally they drew attention to the fact that recent data indicated that aspirin, even in doses as low as 75mg, was still the drug most commonly implicated in admission to hospital for side effect problems and still had a considerable mortality. Their overall concern was therefore that the removal of one product from the market, or the severe restriction of its use might result in no public health benefit with other products that might have a worse overall risk benefit ratio becoming more commonly used. (49)

REPLIES FROM PHARMACY INTERESTS

The **Royal Pharmaceutical Society of Great Britain (RPSGB)** stated that there appeared to be no clinical evidence for any group of people to suggest that the balance of risks and benefits of Co-proxamol was favourable. The Society, however, was aware that there were many people that have taken Co-proxamol for a long period of time either on a regular or when required basis that had strong "belief" in the product. For some, the perceptions on the effectiveness of Co-proxamol could be affected by changing the brand or packaging. This did cause community pharmacy a problem when manufacturers changed the packaging and appearance of tablets when counselling patients and healthcare professionals. Within hospitals for many years there had been an extensive programme, often led by pharmacy, to stop or restrict the use of Co-proxamol. In most hospitals this had been successful. In some hospitals it was available for "restricted" use due to the demands of a limited number of consultants. There were, however, concerns that patients admitted to hospital on Co-proxamol were changed on to another analgesic and when they returned home that they still had stocks of Co-proxamol which they continued to take. This might result in them taking two or more paracetamol combination analgesics and so inadvertently overdosing on paracetamol. The RPSGB was unable to identify any strong reason as to why Co-proxamol should remain generally available but due to the large number of people in the community receiving this product did have concerns over how the withdrawal of this product was managed if this option was chosen. (51)

A senior **Pharmacist at Trent Medicines Information Service** at Leicester Royal Infirmary stated that in 1995 the Leicestershire Formulary Working Party took the view that there was an excessively high use of Co-proxamol in the Leicestershire Hospitals. More Co-proxamol was being used than paracetamol. The decision was taken that the local Prescribing Guide would no longer recommend its use in the light of the poor evidence to support its use and its known toxicity in overdose. Information was prepared and circulated to prescribers and publicity in the form of presentations to doctors. Pharmacists were encouraged to query prescriptions for the product. Since 1996-7, prescribing had dropped to zero in the Leicester hospitals, and prescribing in Primary Care was much lower than previously. (19)

The **Scottish Specialists in Pharmaceutical Public Health Group** would due to a lack of long term efficacy data, together with undoubted safety concerns endorse any plan to withdraw Co-proxamol in a planned and phased fashion to minimise disruption for patients. (31)

The **British Pharmacological Society** shared a significant concern about the hazards of overdose with Co-proxamol which was still one of the three most widely prescribed preparations in the NHS. It was often stated that Co-proxamol had no more efficacy than paracetamol alone. They pointed out that this evidence related to acute use rather than to chronic use and it might be important not to extrapolate to chronic use from the acute experience. Adequate studies of long term use of Co-proxamol in chronic pain versus paracetamol had not been undertaken. They were aware of some hospitals and PCTs who had attempted to remove Co-proxamol from their formularies with varying degrees of success. In general, Co-proxamol had been displaced in these areas by other compound analgesics, which again lacked evidence and might be dangerous in overdose (although in view of the cardiotoxicity of dextropropoxyphene, they might be preferable). This again illustrated the general dictum that it was easier to change what a doctor prescribed rather than whether they would prescribe, and that change in this area would be difficult without clear action. Despite all of this they believed that it would be most appropriate to withdraw the preparation from the market. They thought this should be a gradual process with increasing restrictions to reduce its use. They thought, however, that there was a danger that its use would be replaced by that of other compound analgesics unless there was a very active process of education of both prescribers and patients. (24)

REPLIES FROM SPECIALIST BODIES

The **Pain Relief Foundation's Pain Research Institute** stated that they were aware that dextropropoxyphene had appreciable N-Methyl D-Aspartate (NMDA) receptor antagonistic activity and Amine (Noradrenaline and Serotonin) re-uptake inhibitor activity. Letters regarding this had been published in *Neuroscience* 2000; 295, 21-24. Anecdotal evidence suggested that the combination of dextropropoxyphene and paracetamol had advantages over paracetamol alone in the treatment of mild neuropathic pain and maybe better than the other weak opioids currently available. It was perhaps because of this particular effect that made it popular among patients and indeed it was often the drug that was preferred by patients for mild neuropathic pain problems. They stated that there was obvious greater efficacy of Co-proxamol compared with codeine. It was known that about 10% of the population were unable to metabolise codeine, which was a pro-drug, to its active compound morphine. Clearly the risks had to be balanced against its benefits. Certainly purely from the aspect of postoperative or standard nociceptive pain the risks of dextropropoxyphene clearly outweighed the benefits. They stated it was not clear from the background evidence supplied whether it was the dextropropoxyphene that was the cause of death in overdose or whether it was the paracetamol content that was either directly responsible or had an additive effect especially with dextropropoxyphene. (1)

The **British Pain Society** welcomed the review as it was an area of concern for all who worked in pain management and for patients who might be prescribed this medication. They supported measures to reduce the 300-400 fatalities each year. There had been a big educational initiative in the UK certainly within the

undergraduate and immediate post-graduate medical community to steer doctors away from prescribing Co-proxamol and they assumed that it was not so popular amongst medical practitioners recently qualified. They had concerns regarding the apparently sub-therapeutic dosage of paracetamol in this preparation, even when two tablets were taken, and the effect that this might have on the presumed efficacy. In clinical practice, however, it was apparent that there were certain patients taking Co-proxamol who stated that this drug was efficacious and free from side effects, whereas other drugs, such as Co-codamol 8/500 or 30/500 had not been beneficial or had caused side effects. The reasons for this are unclear. However, this may be due to genetic factors relating to the patient, the type of pain for example for some type of pain e.g. visceral pain in which dextropropoxyphene might be more efficacious than codeine and individual difference in the pharmacokinetics of drugs due to hereditary polymorphisms of drug metabolising enzymes. Cytochrome P4502D6 metabolises codeine (pro-drug) to morphine. About 7-10% of Caucasians lack any CYP2D6 activity due to gene mutation, thus rendering codeine ineffective. If Co-proxamol were to be withdrawn there were a group of patients who would suffer. They supported restricting the indications to second line therapy where other weak opioid analgesics should be started as a first line treatment. However, if the patient failed to respond to these medications, then they believed that it would not be unreasonable for a trial of Co-proxamol for a short period, using specific pain scoring methods e.g. Visual Analogue Score or Numerical Rating Scale, but also monitoring functioning and sleep. They believed that warnings should be strengthened and that there should be a co-ordinated programme of education and communication for healthcare professionals to alter prescribing behaviours. They did not support withdrawal, as they would be concerned that this would deny some patients an appropriate analgesic medication for them and their otherwise intractable pain. (34)

Pain Concern stated that they dealt with about 10 enquiries a day and often these pain sufferers said that they had experienced pain relief with Co-proxamol with no side effects. Many of these patients had not found relief with other medicines they had been prescribed. Pain concern would therefore be opposed to withdrawal of the product, as this would adversely affect the quality of life of many people with chronic intractable pain. (44)

REPLIES FROM MEDICAL INTEREST

An **individual GP** stated that he believed that Co-proxamol should be removed altogether from the Pharmaceutical Schedule, with a six to twelve month period of notice. As a GP he has had to perform mouth to mouth resuscitation to a patient who was apnoeic after self poisoning with Co-proxamol, and had another young patient die after self poisoning with Co-proxamol. He strongly suspected that the prime toxicity in self poisoning related to respiratory depression rather than cardiotoxicity. In these circumstances he saw no justification for continuing its use. (2)

A **doctor in the Navy** stated that he regarded Co-proxamol as a second line medication but his experience was that a population of patients got improved pain relief when changed from other analgesics of similar potency. Where other weak opiates had produced unacceptable adverse effects Co-proxamol sometimes offered improved tolerability. (3)

A **consultant in the Navy** experience with Co-proxamol and its use as a second line analgesic suggested its retention on the basis of what appeared to be an individual idiosyncratic preference by some patients. Additionally patients did not appear to be so troubled by adverse effects and particularly constipation found with the opioids of similar potency. (4)

A **consultant physician in Rheumatology** stated that in whatever way one looked at the suicide figures relating to the use of Co-proxamol, it would be difficult not to conclude that it was and will continue to cause significant harm. He stated that there were other alternatives that were safer and there were other alternatives that were as, if not more, effective. Co-proxamol was not a life saving treatment and product withdrawal possibly over a specified timescale would be a very reasonable course of action to adopt. (5)

A **consultant psychiatrist** and chair of a county suicide prevention task force stated that 13% of all suicides (not just overdoses) were due to either Co-proxamol or dothiepin. On the back of this he worked with the PCT pharmaceutical advisors (and Trust chief pharmacists) to promote safe and appropriate prescribing of these (actually pointing out the dangers and possible alternatives). Virtually all PCTs (6 in all) had now demonstrated a reduction of around 30% in total prescriptions over a 12 month period. (22)

A **GP** stated that there was no doubt that in some patients Co-proxamol did have great benefits. He had several patients with either rheumatoid arthritis or severe osteoarthritis who had been rotated through a variety of analgesics from paracetamol, Co-codamol, dihydrocodeine, tramadol and in one case morphine. However they returned to him saying that Co-proxamol gave them better pain relief with the least side effects. Obviously these patients did not constitute a controlled trial - but for each of these individuals - they had done their own trial and had no doubts about the results. In the 30 years he had been in general practice, none of his patients had used Co-proxamol in overdose. He stated he did not use it for simple aches and pains, which was what the younger people tended to come with. He thought it would be a great loss to a number of his patients if it were to be discontinued. If it was the overdose risk that was the problem he suggested the Agency could restrict it's use to the over 45s as this group were unlikely to abuse it. (23)

A **GP** stated that he had prescribed Co-proxamol since he qualified in 1969. He stated that patients had reported that Co-proxamol provided better pain relief than paracetamol alone although some of the relief might have related to a feeling of relaxation, which must be related to the dextropropoxyphene. In terms of other combination products, Co-dydramol seemed to be more soporific/produce more nausea and constipation, Co-codamol 8/500 did not seem to give adequate pain relief, Co-codamol 30/500 was very popular with the local A&E department, patients in severe pain and drug addicts and finally paracetamol + tramadol was new and seemed to work although he questioned the risk of addiction. In terms of separate products, paracetamol plus codeine was popular with drug addicts as was paracetamol plus dihydrocodeine (short acting) however, nausea and drowsiness could be a problem. Paracetamol plus dihydrocodeine (sustained release) was a very useful product and addicts did not like it as much as it did not give the 'buzz'. Paracetamol plus tramadol again was popular with addicts. If the pack size was restricted there would be

workload issues for GPs and their staff and patients would complain about having to reorder frequently. He thought that avoiding the drinkers would be difficult in an area where alcohol consumption was high and there was a great tradition in South Wales of patients sharing their medication. He stated that the patient information leaflet could be a real disincentive to patients taking any medication if all side effects/adverse effects were listed clearly and patients were advised by the pharmacist to read the leaflet before taking the tablets. Any significant changes to the rules on Co-proxamol prescribing would involve a huge amount of work and much aggravation for GPs and their staff. Changes should be more of a hearts-and-minds operation rather than a ban. Advice on the first choice of an alternative would be helpful to avoid confusion in an area. (26)

The **British Medical Association's General Practitioners Committee** stated that GPs had reported that based on their practise Co-proxamol did have an important part to play. It could be a preferable drug to those containing codeine. Co-proxamol had relatively little constipating effect especially in the elderly, and had much less addictive potential. It caused far fewer 'medicine related' secondary problems in the elderly than the codeine containing drugs. It could be particularly effective in rib pain and pleuritic pain, often more so than Co-codamol 30/500. They said that the research done looking at the effectiveness of Co-proxamol and Co-codamol had showed direct comparisons and had not looked into the role of Co-proxamol in patients who could not tolerate Co-codamol or found it ineffective. It was useful as a second line analgesic without going up the analgesic ladder. There was a limited range of cheap moderate strength analgesics that weren't codeine or an NSAID. While it was accepted that the drug had its dangers it was not felt that it was so dangerous that GPs should not have the choice to prescribe it. (33)

An **arthritis centre consisting of rheumatologists** practising in Northwest London, seeing over 2550 new patients with musculoskeletal (M/S) problems annually stated that most patients had long histories. They recognised that the use of Co-proxamol in chronic M/S pain was under-researched and that they had no evidence, other than their experience, to support its use. The review made no reference to the scale of the prescriptions of Co-proxamol, how many suicides per prescription and the relationships to other drugs that this group of patients would be given, e.g. codeine in any of its many forms. Although self-evident, their primary responsibility was to the patient. The issue as to what happens to prescribed drugs after prescription was a secondary issue. They were, however, confident that rheumatologists would wish to comply with any consensus as to the advice given to patients about the storage of medications and the prevention of suicide. The burden of M/S conditions was enormous and the cardinal symptom was pain. Although disabling pain was often thought to be a problem of the elderly, M/S pain was the commonest reason for manual workers to have longer-term sickness absence; and the second commonest reason for individuals to need incapacity benefits. 22% of the 2.7 million recipients of incapacity benefit had M/S conditions and the Government recognised the importance of pain management in their rehabilitation into work. They stated that rheumatologists recognised that the management of pain was not just a matter of medication, but also of using physical, environmental and psychosocial methods. In spite of this, one of the commonest problems in clinic was that of inadequate pain control, with the resultant reduction in physical activities, and sometimes loss of job or role in life. Few patients referred to this service achieved adequate analgesia with paracetamol, and those that

did were usually discharged back to primary care. Only 1-2 patients per clinic per year stated that they would prefer paracetamol to Co-proxamol. The issues for them therefore related to the management of inflammatory and non-inflammatory M/S pain. In the first group, non-steroidal anti-inflammatory drugs (NSAIDs) are the first line of assistance, although many individuals would need analgesia in addition. For those with spinal pain, or osteoarthritis, they took the view that analgesics probably had a better risk/benefit ratio than NSAIDs over time, although NSAIDs had an important role in the management of acute flares of M/S pain. The next stage up the analgesic ladder was a compound paracetamol preparation, of which those best tolerated appeared to be either Co-proxamol or Co-codamol (with 8mg of codeine). Unfortunately, with their ethnic background of patients, codeine appeared to constipate (and less frequently nauseate) readily, even in small dosage, and so Co-proxamol was frequently prescribed in their clinics for mild to moderate pain. Many patients could live with their pain during the day but found Co-proxamol helpful for nocturnal analgesia. They were concerned that whilst a clear patient preference for Co-proxamol existed, its loss would make a large difference to their ability to help many with mild to moderate M/S pain. (38)

REPLIES FROM PATIENTS

An individual **patient** stated that she took Co-proxamol regularly to manage the pain from osteoarthritis and fibromyalgia. Paracetamol alone did not control her pain and codeine alone was too strong. One of the advantages of Co-proxamol for her was that it did not cause nausea, indigestion or constipation – all of which she got from codeine containing drugs. She was worried that there was a possibility that this drug would become unavailable because a certain number of people chose to kill themselves with it. From the MHRA's information it appeared that the number of accidental deaths was minimal when compared with the 2000 plus deaths annually from anti inflammatory drugs and their complications. (9)

An **individual patient** stated that she suffered extensive life-threatening injuries three and a half years ago. Co-proxamol tablets were prescribed, in addition to morphine by drip. Her GP continued to supply them with the warning, not only that overdose was dangerous but that they could be addictive. Taking that into account, she used them extremely carefully. She still obtained them on prescription because they were far more effective than paracetamol alone. She had absolutely no doubt about that, having tried paracetamol alone for the same pain. She took one dose a week on average for an acute pain in a muscle. Left untreated, this pain would spread, causing what she described as 'close-down' of her whole body. One dose comprising two Co-proxamol tablets, taken at the first sign of this pain stopped it getting worse and eliminated it completely in about an hour. She always took the tablets with food and had noticed no side effects whatsoever at this dosage. When she needed more, in the weeks immediately following the injury, they caused constipation, but this was successfully treated by her GP. She agreed that the warnings on the box were probably insufficient and few people she had met actually read the accompanying leaflets, or understood them. Equally, if someone was intent on suicide, removing these tablets from the market would not stop them. As far as accidental overdose was concerned, her view was that individual GP's who took care to explain the danger was the best safeguard. (20)

An **individual patient** stated that she had been taking Co-proxamol for over 15 years, to treat chronic pain, and was emphatic that paracetamol was not equivalent in terms of pain relief. (21)

REPLIES FROM THE NHS

Solihull Primary Care Trust (PCT) stated that in the last 18 months they had had 3 deaths associated with the misuse of Co-proxamol. It had become apparent that some GPs were not sufficiently aware of the risks associated with prescribing Co-proxamol, especially in patients with a history of alcohol misuse and suicide attempts. It was particularly regrettable that the British National Formulary (BNF) did not currently refer to this in its entry for this drug. Inevitably GPs did not access the medicines leaflet but relied on their previous experience of using this drug in Secondary and Primary care. This PCT had attempted to address this issue over the years but their efforts had only been effective with a significant drop in prescriptions for this drug, now that these deaths have occurred and been publicised. (10)

North Cumbria Medicines Management Group's view was that Co-proxamol was no longer used in the treatment of post-operative pain in either of the acute hospitals in North Cumbria. Their regime comprised paracetamol +/- morphine, then paracetamol +/- codeine, and then paracetamol. The rationale was that the pain relief could be stepped down as the pain became less severe. The acute trusts had always taken a dislike to combination preparations, seeing them as a compromise. The evidence for the efficacy for the long-term use of Co-proxamol was almost non-existent. It was prescribed for some patients over prolonged periods of time, but safer, proven alternatives were available. Co-proxamol contained only 325mg paracetamol, which gave only 60% of the recommended maximum dose of paracetamol a day. Co-proxamol was dangerous in overdose and also in the elderly or in patients with renal impairment. The view of some members was that patients might develop a dependency on Co-proxamol. They believed that product withdrawal over a specified timescale would be the preferred option. Prescribers were unlikely to take notice of restricting the indications and education had been tried in the past, but it was still being used. Withdrawal should be done over a period of 12 to 18 months. (11)

Compton Hospice stated that Co-proxamol was used routinely at Compton hospice for patients with moderate to severe cancer pain. It was used for patients who had got significant constipation from using Co-codamol. The dose was titrated upwards to a maximum of 12 tablets daily but usually patients were changed to a strong opioid drug when they reached a dose requirement of 8 tablets daily. Compton Hospice had developed an expertise in using methadone in patients who developed tolerance to other strong opioid drugs. Since Co-proxamol had a rapid onset of action, it was used during the 3 hours lockout period that they applied to methadone. When patients were established on a regular dose regimen of methadone after the initial titration period, Co-proxamol was used for breakthrough analgesia. They had found that Co-proxamol was effective even in patients who were tolerant to high doses of other opioid drugs. This was likely to be related to the specific activity of dextropropoxyphene, which was likely to be similar to that of methadone. On the issue of safety, they considered that Co-proxamol carried a similar balance of risk to benefits as the strong opioid drugs that they used in the context of severe cancer pain.

It might have a significant reduced toxicity compared to some NSAIDs that might be required if Co-proxamol could no longer be used. Compton Hospice would support a change in the packaging of Co-proxamol to reduce the risk of fatalities in overdoses. (12)

Northumberland NHS Care Trust stated that they ran a prescribing initiative last year, which attempted to reduce the prescribing of Co-proxamol. They then tracked actual prescribing. Reductions in prescribing for the 11 practices in the locality were in the order of 20-30% (comparing the first quarters in 2003 and 2004). Practices ranged between 55% reduction and a 5% increase in prescribing. This would probably be the maximum size of effect a campaign on restricted use would have. Even with this degree of effort a lot of patients remained on Co-proxamol and for this reason they would favour an outright ban. They stated that other less dangerous medicines had been withdrawn from the market for safety reasons. (13)

North Tees PCT asked the review to consider how patients were to be best managed if the review recommended a change in prescribing patterns. In the past, he and his medical colleagues had found that many patients who had been taking Co-proxamol chronically for any length of time, experienced withdrawal effects unless an alternative opiate analgesic was substituted. Paracetamol, might in theory be equipotent but many patients would soon reapply pressure on prescribers to revert back to Co-proxamol. If such circumstances arose, a recognition and recommendation of how best to manage withdrawal would be of use. (14)

The forensic toxicology section of the **Regional Laboratory for Toxicology, Sandwell and West Birmingham NHS Trusts** at City Hospital stated that they provided a specialist service for Coroners in England and Wales. Over the years they noted the relatively high frequency of Co-proxamol related deaths, either alone, or in combination with alcohol or other depressant drugs. In some cases, death appeared to be remarkably rapid, within a few hours of ingestion. Thus, almost all such deaths were seen outside of hospital. Whereas the absolute number of such deaths had remained relatively constant over the last 5 years (about 30 per year) the relative proportion of these deaths had apparently declined to about 3% of all cases referred by Coroners. However, this might reflect changes in referral pattern and case mix. They were unable to comment on the efficacy of Co-proxamol as an analgesic. However, as toxicologists, they had concerns with regard to the relatively high number of acute Co-proxamol related deaths for an analgesic preparation. Moreover, in overdose, Co-proxamol appeared to have a relatively poor margin of safety, entirely related to the presence of dextropropoxyphene. It would be appropriate to further restrict the prescribing of Co-proxamol and recommend the use of safer alternatives. (27)

The Community Health Division of **NHS Ayrshire and Arran** were unable to provide any additional information or data that would help in the evaluation of Co-proxamol. They stated there would be an issue with regard to the management of any restrictions or withdrawal of Co-proxamol given the high number of patients being prescribed in the area. (29)

South and East Dorset Primary Care Trust's pharmaceutical adviser stated that although they did not have any direct evidence of the risks and benefits of Co-

proxamol, given the paucity of clinical trial data and the risk of deliberate or accidental overdose they supported the withdrawal of the drug. If Co-proxamol was a new drug, being looked at by their local drugs committee, the application would be turned down on the basis of poor trial results. As with other PCTs they were looking of ways of reducing the number of suicides, so withdrawing Co-proxamol would be a positive step. (30)

Bedfordshire Heartlands Primary Care Trust's prescribing adviser stated that this issue had been discussed by their Prescribing Subcommittee in relation to their PCT formulary. The Prescribing Subcommittee considered that Co-proxamol should not appear on the PCT formulary, and cited recommendations from the following recognised authoritative sources: NHS Northern and Yorkshire Drug Update 21 October 2000, British National Formulary 47, MeReC 11 1, 2000, Drug and Therapeutics Bulletin 36 10, 1998, British Medical Journal 326 1006-1008 and the NHS Regional Drug and Therapeutics Centre, Newcastle, Drug Update 31, April 2004. They also recommended the MHRA looked at Lancet articles cited in the BMJ article by Hawton et al. The overwhelming body of opinion from these respected sources indicated that it was no longer appropriate to prescribe Co-proxamol routinely, and their PCT had taken the decision to exclude it from their formulary. They would therefore welcome any or all of the "next steps" outlined in the consultation. However, with regard to the final option (withdrawal over a specified timescale), they stated that co-proxamol was currently prescribed to a significant number of patients, and that these patients might well be resistant to change, particularly if they had taken the medication for some time. Withdrawal from the market might therefore give prescribers some difficulty in finding an alternative and in switching significant numbers of patients. The time scale would therefore need careful consideration. (32)

Sheffield Teaching Hospitals NHS Trust on behalf of oncologists and rheumatologists stated that a local senior rheumatologist found that Co-proxamol had proved useful in several patients with chronic pain. The Trust's Medicines Management & Therapeutics Committee (MMTC) had for many years endorsed the practice of discouraging new prescriptions for Co-proxamol and switching patients to alternative analgesics (usually Co-codamol) whenever clinically appropriate. As a result, very little Co-proxamol had been purchased by the Trust's Pharmacy Departments for many years. The main prescribers in this Trust were oncologists and rheumatologists, and with the exception quoted above, no other consultants from either of these specialities expressed strong views on retaining Co-proxamol. In summary, the Trust had attempted to restrict the use of Co-proxamol to those patients with chronic pain for whom previous analgesics had been clinically inappropriate. The view from local acute pain specialists was that this strategy was still valid, and that Co-proxamol indications should be further restricted to be prescribed third or fourth line by pain specialists for patients with otherwise unmanageable chronic pain. In terms of new evidence the toxicology laboratory of the Royal Hallamshire Hospital investigates about 2000 cases a year of fatal Co-proxamol overdoses for Coroners in England and Wales. Not all of these cases were overdoses; as many reflected the investigation of death due to injury while intoxicated. Fatal overdoses with Co-proxamol continued to constitute a significant proportion of this work. Over the last 5 years it had averaged about 40 cases per year. It was clear that many of these deaths resulted from impulsive ingestion of Co-proxamol often in association with

intoxication with alcohol. They questioned the need for the continued availability of this preparation given the number of fatal overdoses associated with its use. (39)

County Durham and Darlington Priority Services NHS Trust provided a report detailing an audit of suicides occurring within County Durham and Darlington. They found that 12.7% (n = 32 out of 205) of all suicides were as a direct result of overdose with Co-proxamol, dothiepin and amitriptyline. Co-proxamol was pre-eminent in 16 of those cases (8% of entire sample) which was a sizeable proportion. (50)

The **Tayside Medicines Unit (on behalf of palliative care physician)** was aware of the long-standing concerns about safety and efficacy in overdose of Co-proxamol. In cancer patients, WHO guidelines indicated the need for the use of opioids for mild to moderate cancer pain. Currently, there is the choice of Co-codamol, dihydrocodeine, Tramadol or Co-proxamol. Co-proxamol was a useful alternative in some patients, especially those who could not tolerate codeine, found tramadol ineffective or were constipated on dihydrocodeine. The Associate Specialist was unaware of any evidence of abuse, overdose or side effect problems with Co-proxamol in the group of patients treated in palliative medicine and would argue for the continued availability of Co-proxamol for mild to moderate pain in palliative care patients. The dose would generally be the maximum prescribable dose, for a period of weeks to months depending upon disease or pain progression. (52)

REPLIES FROM OTHER BODIES

The **Association of Nurse Prescribing** was unable to supply any further evidence on the safety and efficacy of Co-proxamol. Although Co-proxamol was not currently included in the Extended Nurse Prescribers' Formulary many nurse prescribers had indicated that they would find it a useful addition as second-line therapy where paracetamol alone had been ineffective. Some nurse prescribers stated that anecdotal evidence from patients suggested that Co-proxamol was highly effective for some patients. As nurse prescribers would always be encouraged to prescribe or recommend treatment using a firm evidence base they were pleased to see that further scrutiny of this drug was being encouraged. As patient safety was paramount they would support the proposed regulations for, restricting indications, further strengthening of warnings in product information and labelling and introducing smaller pack sizes. There does not appear to be sufficient evidence for withdrawal of the product, and in view of clinicians' anecdotal evidence of good analgesic response in some patients they would not support withdrawal. Although supportive of any education developments relating to prescribing they felt that such programmes should look at a range of drugs (e.g. all analgesics) rather than focussing on single drugs. Such education programmes should include information relating to efficacy, cost-effectiveness, concordance and promote patient involvement in decision making. (35)

Arthritis care stated that for many people with arthritis and musculoskeletal conditions the main symptom was pain. Management of pain was intrinsic to living with arthritis and musculoskeletal conditions. This could be done in a range of ways from appropriate exercise, hydrotherapy and access to medications/treatments. Co-proxamol was one of a range of treatments available in tackling pain management. Others include NSAIDs, COX II's and, for specific forms of arthritis, anti-TNFs. The Medical Advisory Group of Arthritis Care stated that Co-proxamol, when used as a

combination treatment for people with arthritis kept the number of drugs down to a minimum, particularly when polypharmacy was a regular feature and when cognitive function could be an issue (This would be mainly in the elderly due to early signs of dementia). Many people with arthritis and musculoskeletal conditions, of which a high percentage would be elderly, were at risk of constipation and peptic ulcers from the alternative medications available. Many older people with arthritis were contraindicated for NSAIDS or COX II's and were reliant on Co-proxamol in their pain management. The use of Co-proxamol and low dose opiate was more effective than paracetamol and NSAIDS. People with arthritis and musculoskeletal conditions were not the ones primarily at risk of suicide from Co-proxamol abuse and it would seem unfair to deny them access to an effective medication to manage their pain. The use of Co-proxamol was not limited to the arthritis and musculoskeletal community but was used in orthopaedics, pain clinics and palliative care due to lack of side effects. It should be noted that the suicide risks of Co-proxamol were due to the toxicity of the drug, not a side effect. As such there were issues concerning prescribing, information and packaging that could go some way to tackle this issue. It would not be wise to deny access to Co-proxamol to people who might derive real benefit from it because of concerns about the potential for abuse of the drug. As such Arthritis Care would support the recommendations i, ii, iii, iv in the Next Steps section of the consultation document, but would strongly oppose the withdrawal of Co-proxamol. Arthritis Care recognised that there was some concern regarding the suicide risk associated with Co-proxamol and would welcome measures to ensure that it was prescribed safely. (45)

The **British Society for Rheumatology** stated that with respect to the two key concerns about Co-proxamol, that it had been used in many suicide attempts and that it was questionable whether it was any more effective than paracetamol alone, offered the following comments. As discussed in the epidemiological data provided in Annex A of the document, the largest proportion of suicide attempts were made by those in the 10-24 year old age group, however, Co-proxamol was mostly used as a long-term treatment for osteoarthritis. Most of these patients were substantially older and statistically far less likely to attempt suicide. It would therefore seem that the problem was that Co-proxamol was getting into the wrong hands. With respect to the efficacy of Co-proxamol there was some evidence that it worked when paracetamol did not, however this evidence was rather limited. These drugs had been around for nearly 40 years and would not have been subjected to the major drug trials that would be done today if these were new drugs being introduced in the present day. However, Co-proxamol had maintained its place and still appeared on most hospital formularies. It was clear that the situation with respect to Co-proxamol might not be satisfactory by today's standards, however, their recommendation was that the drug was only prescribed where paracetamol alone had failed and was not prescribed to those with a history of severe depression. Efforts should be made to keep the drug out of reach of those that it was not intended for. They would also suggest that greater evidence about efficacy needed to be gathered before product withdrawal would be justified. (46)

The National Association of Private Ambulance Services (NAPAS) supported any proposal. (18)

The Association of the chief Police Officers in Scotland had no adverse comments to make. (28)

The **National Council of Women** supported the introduction of smaller pack sizes for Co-proxamol. They considered that Co-proxamol should be a prescription only drug and believed that it gave wider prescribing choice, but guidance to family doctors was needed on account of its dangers. Most doctors would prescribe as large a quantity as appropriate to save the patient money on prescription charges. With regards to the suicide rates attributed to Co-proxamol, they pointed out that if Co-proxamol was not available suicidal persons would use paracetamol and aspirin. Most wouldn't choose a specific analgesic. Accidental deaths were of much more concern. (40)

Annex 6

Documentation provided
separately.

Annex 7

SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the Medicinal Product

'DISTALGESIC' CO-PROXAMOL Tablets

2 Qualitative and Quantitative Composition

Each tablet contains 32.5mg Dextropropoxyphene Hydrochloride BP (equivalent to approximately 30mg dextropropoxyphene base) with 325mg Paracetamol Ph. Eur.

3 Pharmaceutical Form

White, pillow-shaped, film-coated tablets.

4 Clinical Particulars

4.1 Therapeutic indications

Actions: Dextropropoxyphene is a mild narcotic analgesic structurally related to methadone.

Indication: For the management of mild to moderate pain. Distalgesic should only be used when first line analgesics have proved ineffective or are inappropriate.

4.2 Posology and method of administration

For oral administration to adults only. The usual dose is 2 tablets three or four times daily and should not normally be exceeded. Take every 6-8 hours, as required.

Consideration should be given to a reduced total daily dosage in patients with hepatic or renal impairment.

The elderly: There is evidence of prolonged half-life in the elderly, so reduction in dosage should be considered.

Children: Distalgesic is not recommended for use in children.

4.3 Contraindications

Hypersensitivity to dextropropoxyphene or paracetamol and/or any other constituents.

Use in patients who are suicidal or addiction-prone.

Use in individuals who are alcohol-dependent or who may consume alcohol whilst taking Distalgesic.

4.4 Special warnings and special precautions for use

Warnings

All patients must be instructed never to exceed the recommended dose.

All patients must be instructed never to consume alcohol whilst taking a course of Distalgesic. ~~PATIENTS SHOULD BE ADVISED NOT TO EXCEED THE RECOMMENDED DOSE AND TO AVOID ALCOHOL.~~

Dextropropoxyphene products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon and can occur within 15 minutes. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of Distalgesic alone, or in combination with other drugs.

Distalgesic should not be taken with any other paracetamol-containing products.

Overdosage may damage the liver, due predominantly to the accumulation of intermediate metabolites of paracetamol which cause hepatic necrosis. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage. Compared to the general population, the hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Distalgesic should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquillisers, muscle relaxants, antidepressants or other CNS-depressant drugs; patients should be advised of the additive depressant effects of these combinations. Distalgesic should also be prescribed with caution in patients who use alcohol in excess.

Drug dependence: Dextropropoxyphene, when taken in higher than recommended doses over long periods of time, can produce drug dependence.

Precautions

Distalgesic should be administered with caution to patients with hepatic or renal impairment since higher serum concentrations or delayed elimination may occur.

4.5 Interaction with other medicaments and other forms of interaction

Drug interactions: The CNS-depressant effect of dextropropoxyphene is additive with that of other CNS depressants, including alcohol.

Dextropropoxyphene may interfere with the metabolism of antidepressants, anticonvulsants and warfarin-like drugs. Severe neurological signs, including coma, have occurred with concomitant use of carbamazepine.

Speed and/or extent of absorption may be altered by other agents with substantial gastrointestinal effects; for example, metoclopramide or domperidone may speed passage from the stomach to the intestines; and cholestyramine may reduce absorption.

4.6 Pregnancy and lactation

Pregnancy: Safety in pregnancy has not been established relative to possible adverse effects on fetal development. Withdrawal symptoms in neonates have been reported following use during pregnancy. Therefore, Distalgesic should not be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Nursing mothers: Low levels of dextropropoxyphene have been detected in human milk. In postpartum studies involving nursing mothers who were given dextropropoxyphene, no adverse effects were noted in the infants. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

4.7 Effects on the ability to drive and use machines

Ambulatory patients: Dextropropoxyphene may impair abilities required for tasks such as driving a car or operating machinery. The patient should be cautioned accordingly.

4.8 Undesirable effects

The most frequently reported have been dizziness, sedation, nausea and vomiting. Some of these side-effects may be alleviated if the patient lies down.

Other side-effects include constipation, abdominal pain, rashes, light-headedness, headache, weakness, euphoria, dysphoria, hallucinations and minor visual disturbances.

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Dextropropoxyphene therapy has been associated with abnormal liver function tests and, more rarely, with instances of reversible jaundice (including cholestatic jaundice).

Hepatic necrosis may result from acute overdose of paracetamol. In chronic alcohol abusers, this has been reported rarely with short-term use of paracetamol dosages of 2.5 to 10g/day. Fatalities have occurred.

Renal papillary necrosis may result from chronic paracetamol use, particularly when the dosage is greater than recommended and when combined with aspirin.

Subacute painful myopathy has occurred following chronic dextropropoxyphene overdosage.

Chronic ingestion of dextropropoxyphene in doses exceeding 720mg per day has caused toxic psychoses and convulsions.

4.9 Overdose

Initial consideration should be given to the management of the CNS effects of dextropropoxyphene overdosage. Resuscitative measures should be initiated promptly.

Dextropropoxyphene: In the acute phase dextropropoxyphene produces symptoms typical of narcosis, with somnolence or coma and

respiratory depression, sometimes with convulsions. Blood pressure falls and cardiac performance deteriorates. Cardiac arrhythmias and conduction delay may be present. A combined respiratory-metabolic acidosis occurs, which may be severe if large amounts of salicylates have also been ingested. Death may occur.

Naloxone will reduce the respiratory depression and 0.4-2mg iv should be administered promptly. (This may be repeated at 2-3 minute intervals, but if there is no response after 10mg of naloxone the diagnosis should be questioned.) The duration of antagonism may be brief and need repeating for up to 24 hours. Mechanical ventilation, with oxygen may be required, and PEEP ventilation is desirable if pulmonary oedema is present.

Blood gases, pH and electrolytes should be monitored and electrocardiographic monitoring is essential. Ventricular fibrillation or cardiac arrest may occur. Respiratory acidosis rapidly subsides as ventilation is restored and hypercapnoea eliminated, but lactic acidosis may require iv bicarbonate for prompt correction. In addition to the use of a narcotic antagonist, the patient may require titration with an anti-convulsant to control convulsions. Gastric lavage may be useful and activated charcoal can absorb a significant amount of ingested dextropropoxyphene.

Treatment of dextropropoxyphene overdose in children: See general comments above. Naloxone at 0.01mg/kg body weight iv should be administered promptly. If there is no response a dose of 0.1mg/kg iv may be used.

Paracetamol: Overdose symptoms may not become apparent until later but early measurement of paracetamol levels is essential. Oral methionine or intravenous N-acetylcysteine given as early as possible is effective in reducing the toxic effects of paracetamol and may have a beneficial effect up to at least 48 hours after the overdose. Treatment should be instituted within 16 hours of ingestion. Symptoms in the first 24 hours are pallor, anorexia, nausea, vomiting, profuse sweating, malaise and abdominal pain. However, the patient may have no symptoms. Abnormalities of glucose metabolism and metabolic acidosis may occur.

Subsequent evidence of liver dysfunction may be apparent up to 72 hours after ingestion, and if severe lead to irreversible hepatic necrosis and death within 3-7 days. Hepatic toxicity has rarely been reported with acute overdoses of less than 10g. However, liver damage is possible in adults who have taken 10g or more of paracetamol. In

severe poisoning, with greater than 15g, hepatic failure may progress to encephalopathy, coma and death.

Cardiac arrhythmias and pancreatitis have been reported.

Acute renal failure may accompany the hepatic dysfunction and can occur without signs of fulminant hepatic failure. Typically renal impairment is more apparent 6-9 days after overdose.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

The product is a compound analgesic containing the non-narcotic drug (paracetamol) for the relief of pain of musculoskeletal conditions and a narcotic drug (dextropropoxyphene) for the relief of pain of visceral origin.

5.2 Pharmacokinetic properties

Single dose studies have shown peak plasma levels of 0.06mg/l two hours after administration of 65mg of dextropropoxyphene HCl. Variation of plasma levels between subjects may be due to individual differences in drug absorption and metabolism.

Multiple dose studies have shown that differences in plasma levels obtained with the hydrochloride salt or the napsylate salt have little therapeutic significance and that a 65mg dextropropoxyphene HCl dose administered six hourly will achieve steady state plasma levels in the 0.13 - 0.19 mg/l range after 48 hours. The minimum lethal dose of dextropropoxyphene has been reported to be 500-800 mg and could result in blood concentrations of 0.45 - 0.74 mg/l. Mean half lives of 11.8 hours for dextropropoxyphene and 36.6 hours for norpropoxyphene have been demonstrated.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber in addition to that summarised in other sections of the Summary of Product Characteristics.

6 Pharmaceutical Particulars

6.1 List of excipients

Maize Starch
Pregelatinised Maize Starch
Magnesium Stearate
Methylhydroxypropylcellulose 15
Glycerol
Titanium Dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

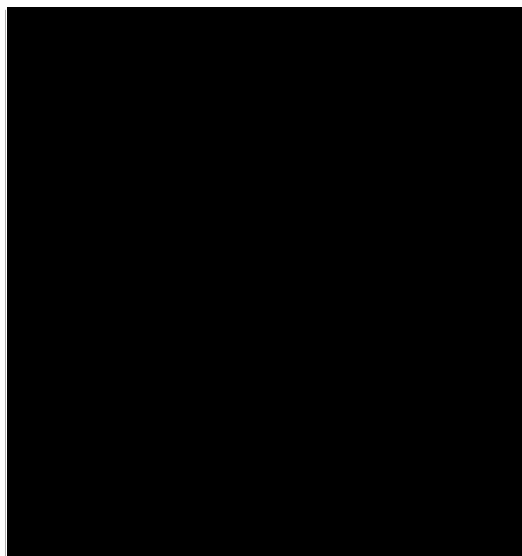
6.5 Nature and contents of container

Blister packs containing 100 white, pillow-shaped, film coated tablets, 14 mm in length and marked 'DG' (10 strips of 10 tablets).

6.6 Instructions for use and handling

None.

7 Marketing Authorisation Holder





8 Marketing Authorisation Number(s)

PL19477/0011.

9 Date of First Authorisation/Renewal of Authorisation

Date of first authorisation: 24th May 1973
Date of last renewal of authorisation: 18th March 2003.

10 Date of Revision of the Text

30th September 2003.

Legal Status

POM



BN:
Exp:

00000
42 X 30 X 101



Co-proxamol Tablets
Each tablet contains Paracetamol 325mg and Dextropropoxyphene 32.5mg.
For oral administration. Take as directed by your doctor. NEVER EXCEED THE STATED DOSE.
Please read the enclosed leaflet carefully before use. Do not store above 25°C.
An overdose of this medicine can be fatal (lead to death).
• Never take more than your doctor has told you to
• Never drink any alcohol whilst taking this medicine
• Return any unused medicine to your pharmacist
Contains paracetamol.
Do not take with any other paracetamol-containing products.

Co-proxamol Tablets

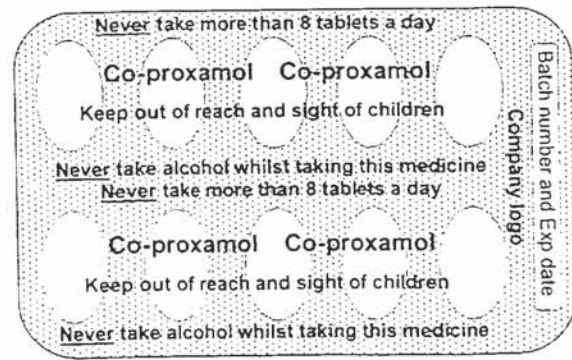
Co-proxamol Tablets

paracetamol and dextropropoxyphene
24 Tablets

An overdose of this medicine can be fatal (lead to death)

- Never take more than your doctor has told you to
- Never drink any alcohol whilst taking this medicine
- Return any unused medicine to your pharmacist

Co-proxamol Tablets



CO-PROXAMOL TABLETS

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and should not pass it on to others.
- It may harm them, even if their symptoms are the same as yours.
- Your doctor may have given you this medicine before from another company and it may have looked slightly different. Either brand will have the same effect.

In this leaflet:

1. What co-proxamol is and what it is used for
2. Before you take co-proxamol
3. How to take co-proxamol
4. Possible side effects
5. Storing co-proxamol

The name of this medicine is Co-proxamol Tablets (referred to as co-proxamol throughout this leaflet). Each tablet contains 325mg Paracetamol and 32.5mg Dextropropoxyphene Hydrochloride as the active substances. The other ingredients are maize starch, pregelatinised starch, croscarmellose sodium, talc, methylhydroxypropyl cellulose, stearic acid, titanium dioxide, povidone, silicon dioxide, macrogol and croscarmellose sodium.

DUMMY

1. WHAT CO-PROXAMOL IS AND WHAT IT IS USED FOR

Co-proxamol tablets are white capsule shaped tablets marked S10 on one side and STERWIN on the other. They are supplied in cartons of 24 tablets.

Co-proxamol is a pain killer. It is used to treat short-term episodes of mild to moderate pain.

2. BEFORE YOU TAKE CO-PROXAMOL

Do not take this medicine if you:

- are allergic to paracetamol, dextropropoxyphene or any of the other ingredients in these tablets.
- are an alcoholic or a drug addict

Co-proxamol is not recommended for children.

Special care is needed (check with your doctor) if you:

- have severe liver or kidney problems
- have alcoholic liver disease
- are taking any anti-depressants
- if you suffer from depression or any other psychiatric condition
- if you have suicidal thoughts
- are pregnant or think you may be pregnant

If you suffer from any of the above, you should discuss with your doctor before taking co-proxamol tablets.

Pregnancy
Co-proxamol is not recommended if you are pregnant, planning a pregnancy or think you might be pregnant.

Breast-feeding

You must not take co-proxamol if you are breast-feeding.

Driving and using machines:

Co-proxamol may cause drowsiness and/or dizziness. If affected you should not drive or operate machinery.

Taking other medicines:
If taken with some other medicines, the effects of co-proxamol or the effects of the other medicine may be increased.

In some cases this may be dangerous and lead to overdose. An overdose of this medicine can be fatal (lead to death).

Please check with your doctor if you are taking any of the following:

- cholestyramine
- metoclopramide (used to treat migraine)

- domperidone - used to treat nausea and vomiting)
- antidepressant therapy
- anticoagulant therapy - used to thin the blood (e.g. warfarin)
- anticonvulsants - used to treat epilepsy fits or convulsions
- drugs which make you sleepy or drowsy

Never take any other medicines containing paracetamol whilst taking these tablets, as this may lead to overdose. Immediate medical advice should be sought in the event of an overdose of paracetamol, even if you feel well, because of the risk of delayed, serious liver damage. Please inform your doctor or pharmacist, even if these statements were applicable to you at any time in the past or if you are taking, or have recently taken, any other medicine - even those not prescribed.

3. HOW TO TAKE CO-PROXAMOL

Adults and the elderly

Swallow the tablets with a drink of water.

The adult dose is 2 tablets, 3 or 4 times a day. Never exceed this dose. This dose may need to be reduced in patients with liver or kidney problems, as there is a risk of overdose.

Children

Co-proxamol is not recommended for use in children.

Important information about taking co-proxamol:

You should never:

- take more tablets than your doctor has told you to take, as this may cause you to overdose.
- take more than 2 tablets at one time or more than 8 tablets a day as this may cause you to overdose.
- drink any alcohol whilst taking co-proxamol. When taken with alcohol, the effect of your tablets may be dangerously increased and can lead to overdose.
- take any other medicines containing paracetamol whilst taking these tablets.

An overdose of this medicine can be fatal (lead to death).

If you take more co-proxamol than you should:

An overdose of this medicine is very dangerous, and can lead to death very quickly (sometimes within one hour). If you or someone else has taken an overdose go to the nearest hospital casualty department immediately. Remember to take any remaining tablets and the tablet box with you.

If you forget to take co-proxamol:

If you forget to take a dose at the right time, take it as soon as you remember, then go on as before. Do not take two doses at the same time.

Effects when treatment with co-proxamol is stopped:

Chronic usage of co-proxamol may lead to tolerance and dependence. If you have taken co-proxamol over a long period of time you should not increase the dosage nor suddenly stop your treatment without discussing this with your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, co-proxamol can have side effects. These include nausea (feeling sick), vomiting, dizziness, tiredness, stomach pain, constipation, rash, headache, weakness, light-headedness, small changes in your vision and changes in mood. There have been a few reports of blood problems associated with paracetamol containing product, but these were not necessarily due to paracetamol. If you experience any severe or unusual effects stop taking co-proxamol and tell your doctor as soon as possible.

5. STORING CO-PROXAMOL

Keep your medicine in a safe place out of the reach and sight of children.

Once you have finished your treatment with co-proxamol, you should return any unused tablets to your pharmacist as soon as possible, for safe disposal. You should never store unused tablets in your medicines cabinet, as they can be dangerous if you leave them where other people may be able to take them. An overdose of this medicine can be fatal (lead to death).

Do not store above 25°C. Store in the original pack.

Do not take this medicine after the expiry date, which you will find on the pack.

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This leaflet was last updated in August 2004.

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