COMMITTEE ON SAFETY OF MEDICINES CSM 2004/16th

NOT FOR PUBLICATION

RESTRICTED - COMMERCIAL	**PL NUMBER:** Several
TITLE OF PAPER: RISK:BENEFIT OF CO-PROXAMOL PRODUCTS	
RISK: BENEFIT ASSESSMENT **PART I:** Responses to public request for evidence on risks and benefits **PART II:** MAH Appeal Pre-hearing For advice	**THERAPEUTIC CLASSIFICATION:** Analgesic
LICENCE HOLDER: Several	**PRODUCT NAMES:** Co-proxamol Distalgesic Cosalgesic Dolgesic
ACTIVE INGREDIENT: Dextropropoxyphene + paracetamol	**PREVIOUS CONSIDERATION BY CSM:** 1985 2004/8th
LEGAL STATUS: POM	**CONSIDERATION BY OTHER COMMITTEES:** SCOP 2004/2nd
SALE/SUPPLY: POM	**ASSESSORS:** [redacted]

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EXECUTIVE SUMMARY

Purpose of the paper

Following earlier consideration by CSM on the risks and benefits of Co-proxamol, this paper presents as Part I the outcome of the public consultation, and as Part II the written information provided by the MAHs as part of their appeal to the CSM 'minded to revoke' letter.

Part I Outcome of consultation

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- A key point voiced by many respondents was that if co-proxamol were withdrawn, this should be done gradually in order to minimise disruption whilst alternative pain management strategies are established for individual patients.

Part II MAH appeal

Meda Pharmaceuticals will present the Committee at a hearing scheduled for 10 November an overview of the risk:benefit of co-proxamol and their proposals for changes to the product information and other measures aimed at reducing the risk of suicide and accidental self-poisoning.

In advance of the hearing, a review of the written appeal is presented made by Meda Pharmaceuticals. Meda is the marketing authorisation holder (MAH) for Distalgesic acting jointly for themselves and on behalf of MAHs for some other co-proxamol products. In essence this positions co-proxamol as second line use, not specifically defending acute use.

Advice sought

The Committee is asked to consider the MAH appeal and to advise on any necessary regulatory action to address the risk:benefit of co-proxamol and appropriate measures to improve safety.

PART I

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 (**Annex 2**) 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 (**Annex 3**) 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* (**Annex 4**) 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 (listed in **Annex 5**), 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
TOTAL	**52**

A detailed list of responses is at **Annex 5.** 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 (11, 13, 24, 29, 30, 31, 32), the Royal College of Anaethetists (41) and a GP (2) and a rheumatologist (5).

The Royal Pharmaceutical Society of Great Britain (51) 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 (47).

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 (48) 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 (3, 4, 9, 23, 26, 38, 39, 46, 52) together with the Royal College of Physicians of Edinburgh, The British Pain Society and patient/carer organisations (43, 14, 34, 44, 45) 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 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 (3), the BMA GPs' Committee (33) and three individual patients responding to the MHRA request for information (9, 20, 21)

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 (1) 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 (12) 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 (10, 13, 19, 22). 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>60years.

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, 35, 3, 46 and 51.

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.

PART II

JOINT MAH APPEAL LED BY MEDA PHARMACEUTICALS LTD

MAHs also participating in this joint appeal are:-
C P Pharmaceuticals Ltd
Sandoz Ltd
Sterwin Medicines Ltd
None of the other MAHs for dextropropoxyphene containing products stated that they wished to appeal but they would be bound by the final CSM decision. The CSM letter to MAHs is at **Annex 1** and their joint response is at **Annex 6** (this item is provided separately from the main paper). For ease of reference, please note that numbers shown in superscript in the text of this section of the assessment report indicate the relevant pages in the MAH response document.

The response document was provided by the MAHs on 30 September 2004, one month later than originally planned. Their reason for this delay was that extra time was needed to co-ordinate activities with the participating MAHs. They have also been given the opportunity to consider and respond to non-confidential responses to the public consultation.

II (1) Points raised in CSM letter of 4 June 2004

The MAHs addressed all the points raised by CSM:-

Safety

2.1 Co-proxamol in overdose has been shown to be highly toxic and a proportion of deaths (approximately one fifth) are classified as accidental. While there is variability in the range and estimates of fatal co-proxamol doses, as few as 6 co-proxamol tablets have been considered sufficient to cause a fatal outcome.

The MAHs attempted to use the ADROIT drug safety database to compare the safety in overdose of co-proxamol versus other analgesics[10-12]. However, whilst there have been approximately 300-400 certified deaths each year for the past 20 years associated with co-proxamol overdose, only one such fatality has been reported into the ADROIT database since 1963. This is because whilst ADROIT is a useful signal generation tool, it is not capable of providing meaningful data to formally evaluate safety signals or compare the safety of one drug with another.

The MAHs discuss US study data showing that dextropropoxyphene overdose fatalities were due to suicide or abuse, concluding that the underlying psychiatric problems of the deceased were major contributory factors to suicide ideation and that dextropropoxyphene was safe when used as properly prescribed.

Assessor's comment:
The circumstances under which dextropropoxyphene is used abroad are not necessarily similar to co-proxamol usage in the UK.

*As patients with chronic pain are at risk of depression, the risk of suicide in 'legitimate' co-proxamol users is a cause for concern. UK data have shown that after correcting for population age distribution, the elderly are the age group at greatest risk of co-proxamol related suicide and the least risk group is 0-19 year-olds. (**Annex 2** CSM 2004/8th, page 20).*

Whilst acknowledging that there is a great deal of variability between individual patients and taking into account the uncertainty regarding therapeutic, toxic and fatal levels of dextropropoxyphene , the MAHs concluded that the quantity of co-proxamol required to produce a toxic dextropropoxyphene plasma concentration is 20-25 tablets[16] (i.e. 2 days' supply).

2.2 There are additive toxic effects when co-proxamol is taken with alcohol and / or other central nervous system depressants.

The MAHs noted the report of fatal overdose involving possibly as few as 6-8 tablets in combination with alcohol (this increases dextropropoxyphene bioavailability by approximately 25%) and were able to concede that 15-20 tablets can be fatal in the presence of alcohol or other CNS depressants[18]

Assessor's comment:
The MAHs have acknowledged that as little as 2-3 days' supply of co-proxamol represents a potentially fatal overdose.

2.3 Dextropropoxyphene may be cardiotoxic due to sodium channel blockade and prolongation of the QRS interval, resulting in cardiac arrhythmia.

The MAHs discuss animal data[19] and conclude that at recommended dosage, cardiotoxicity does not appear to be a problem in man. They do not address Bateman and Afshari's published case report and discussion of the cardiac effects of co-proxamol overdose considered by CSM in April 2004 (**Annex 2**).

2.4 The current warnings and advice to health professionals on the use of co-proxamol, strengthened in 1985, have not been shown to be effective in preventing adverse effects, including fatalities associated with co-proxamol.

The MAHs considered that previous strengthening of warnings failed to achieve the required effect because they vary from one product to another and are generally inadequate. The proposed SPC, PIL and label are at **Annex 7**. In addition, the MAHs proposed that pharmacies could generate supplementary warning labels. The strengthened PIL and labelling address the following topics:

- Co-ingestion of alcohol
- Maximum permitted daily dose
- Risk of fatality with overdose (this warning could be a double-edged sword, see comment below)

The MAHs identified several deficiencies in the content and readability of the current product information for the current Sterwin items and the proposed product information were subjected to readability testing in 24 testers aged 10-89 years[24]. There was a bias towards testers aged 16-25 years on the erroneous rationale that people of this age range are statistically more likely to die from a co-proxamol overdose.

Assessor's comment:
ONS data show that fewer than 5% of co-proxamol fatalities were in people aged <20 years so testing may have focused on the wrong age group.

When young people do take overdoses, they often do so at a time of crisis and use co-proxamol that has been prescribed for somebody else. In view of these circumstances, it may be hazardous to display a recipe for successful suicide on the label or product information. Similarly, elderly chronic pain sufferers may regard this information as an invitation to put an end to their problems.

The methodology for reader testing was flawed (e.g. testing was questionnaire-based rather than by interview, some questions were badly framed and the order of questioning was inappropriate; no marking scheme was provided). The proposed PIL, blister strips and label require several amendments, nonetheless we agree with the MAHs that clearer warnings could help to prevent accidental fatalities and the readability testing of patient information is to be applauded.

Efficacy

2.5 There is no robust evidence to support the efficacy of co-proxamol in the management of chronic pain syndromes.

Absence of efficacy in acute use was said to be irrelevant to the use of co-proxamol in the management of chronic pain because there is a strong pharmacokinetic basis to support the position that repeated doses of co-proxamol are more likely to be effective than single doses. Therefore the MAHs contend the meta-analysis by Li Wang Po and Zhang (considered by CSM in April 2004) is not directly relevant to the use of co-proxamol as even acute pain involves repeat dosing.

Assessor's comment:
Failure to demonstrate efficacy superior to full strength paracetamol in single dose studies may not be relevant to efficacy in chronic use. However this lack of relevance does not imply that co-proxamol will necessarily have greater efficacy in chronic use.

It is pharmacokinetically plausible that co-proxamol may have greater efficacy after repeat dosing as dextropropoxyphene tends to accumulate over the course of a few days.

The MAHs also discussed the in vitro NMDA antagonistic activity of dextropropoxyphene and its role in the treatment of neuropathic pain

Assessor's comment:
The postulated role of NMDA antagonism in the treatment of this type of pain is not unique to dextropropoxyphene. There are already well established treatment options for neuropathic pain such as valproate, carbamazepine and tricyclic antidepressants, at least some of which may act through this mechanism.

The MAHs contended that although there is a lack of data from randomised controlled trials, 40 year's extensive use in clinical practice could not be disregarded. They referred to the responses from doctors, nurses and patients received in response to the public request for information as anecdotal evidence of efficacy superior to paracetamol alone.

2.6 There is no robust evidence for synergy of paracetamol with dextropropoxyphene, and therefore its rationale as a fixed combination product requires to be supported.

The MAHs discussed the rationale for combination products in general and state that the combination of paracetamol with dextropropoxyphene in co-proxamol was developed to provide increased efficacy without worsening side effects. Various studies and meta-analyses of mainly single dose studies comparing various analgesic strategies were presented. Only one paper by Gruber[36] was offered as evidence that paracetamol+dextropropoxyphene had greater efficacy (in acute postpartum pain) than paracetamol alone. This research, published in 1977 was a poorly designed synthesis of 6 separate studies using the same protocol. The author concluded that it lacked the sensitivity to show significant differences between the comparators (placebo, dextropropoxyphene, paracetamol 650mg and co-proxamol).

Assessor's comment:
There is no evidence that co-proxamol (paracetamol 650mg + dextropropoxyphene 65mg) has greater analgesic efficacy than paracetamol 1000mg.

As paracetamol 1000mg is generally well tolerated, there is little safety benefit in reducing the dose to 650mg. Therefore it is likely that some paracetamol efficacy is sacrificed in return for no appreciable paracetamol-related safety gain in the combination product whilst adding significant dextropropoxyphene-related hazard and no demonstrable increase in analgesic effect.

2.7 The evidence from acute dose studies is that co-proxamol has not been shown to be more effective than paracetamol 650mg or 1000mg alone.

No relevant new evidence is presented. The MAHs have compiled a tabulation of a heterogeneous collection of 13 mainly multidose studies[40-44] comparing co-proxamol with various other analgesics such as naproxen, co-codamol and meptazinol (which is indicated only for severe postoperative pain). Efficacy and safety results were somewhat mixed although the former tended not to favour co-proxamol.

Use in chronic pain is discussed extensively but no argument has been offered in support of use in acute pain.

Assessor's comment:
The MAHs repeatedly argue on pharmacokinetic grounds that whilst co-proxamol has failed to demonstrate efficacy superior to paracetamol alone in acute dosing studies, co-proxamol might be expected to have greater efficacy with chronic dosing. Therefore, if co-proxamol is of little value in acute pain, e.g. minor accidental or surgical trauma, it would be rational to remove use in acute pain.

Risk:Benefit

2.8 Having regard to the available efficacy and safety data, the benefits associated with co-proxamol in the authorised indications can no longer be considered to outweigh the risks.

A combined response was provided to 2.8 and 2.9 [46]. The MAHs assert that "*the risk:benefit ratio of co-proxamol when used at recommended doses under conditions of normal use is favourable and proven through almost 40 years of use. This position is consistent across all indications and populations*". They state that data has been presented that provides evidence that co-proxamol is efficacious in both acute and chronic pain and that the overall positive balance of the data and the amount of anecdotal evidence should not be ignored.

Assessor's comment:
That co-proxamol has greater analgesic efficacy than placebo is not in dispute. The risk:benefit problem with co-proxamol is that it has a very narrow safety margin-as little as 2-3 day's supply represents a potentially fatal overdose and when viewed in the context of poor evidence of efficacy superior to full dose paracetamol alone, 300-400 fatal self-poisonings annually are not acceptable.

The MAHs state that:- *When used in accordance with the recommendations in the approved SmPC, i.e. a dosage of 2 tablets, 3-4 times a day, co-proxamol is a very safe and effective treatment for mild to moderate pain*[8]. This assertion does not address CSM's concerns about the risk:benefit of co-proxamol because as discussed above, efficacy has not been adequately demonstrated and safety concerns relate to its toxicity when misused.

2.9 The Committee does not consider that the balance of risks and benefits could be made favourable by restricting use to particular populations or indications. In particular, there is no evidence to support restriction of the indications to patients intolerant of, or unresponsive to, other drugs.

The MAHs propose that co-proxamol should be restricted to second line use only; the proposed wording of SPC section 4.1 is in its entirety:-

Actions: Dextropropoxyphene is a mild narcotic analgesic structurally related to methadone.
Indications: For the management of mild to moderate pain. Co-proxamol should be used when first line analgesics have proved ineffective or are inappropriate.
This is hardly a restriction as despite the absence of evidence of efficacy superior to traditional first line agents, most use is 'second line'.

Assessor's comment:
The statement "Co-proxamol should be used when first line analgesics have proved ineffective or inappropriate" does not clearly define what constitutes a first line agent. Although co-proxamol should certainly not be used unless maximal doses of paracetamol (1g four times daily) have proved ineffective, second-line use would not be endorsed unless there is evidence that co-proxamol has superior efficacy to other first line agents.

Also, as discussed at 2.7, there is no justification for acute use.

The MAHs were keen to point out that alternative analgesics had safety problems of their own that could for many patients make them less suitable than co-proxamol. Co-proxamol is not entirely free from side effects. Section 4.8 of the current SPC for Distalgesic (PL19477/0011) states:
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.
cfunction 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.

In addition, the ADROIT safety database for co-proxamol contains several reports of unlisted reactions such as tremor (16), syncope (18), dizziness (78), confusional state (17), drug dependence (24), psychotic disorder (4), abnormal dreams (6) and pruritis (33) which should be addressed in the product information.

The well-established association between NSAIDs and fatal haemorrhagic adverse effects limits their usefulness as an alternative to co-proxamol in susceptible patients. The gastrointestinal side effects of other weak opioids such as codeine and dihydrocodeine alone or in combination with paracetamol, especially constipation, can be a major problem, especially in the elderly. However, it should be noted that co-proxamol is not entirely free from these gastrointestinal effects.

Assessor's comment:
Although it is traditionally assumed to be a 'stronger' analgesic there is no objective evidence that co-proxamol represents a step up the pain control ladder from full dose paracetamol.

Until co-proxamol is shown to have greater analgesic efficacy than full dose paracetamol, the alternative treatment against which the safety of co-proxamol should be measured is paracetamol 1000mg.

II (2) Other safety measures proposed by MAHs

II (2.1) Introduce a smaller pack size

A 24-tablet pack size is proposed so that after treatment of an episode of pain, patients do not store large quantities of co-proxamol for future use. This dose seem a rational measure if co-proxamol is to remain available for acute use. However, in view of safety concerns it is not rational to initiate co-proxamol in patients who are not already chronic users. Also, it should be borne in mind that when taken in combination with alcohol, as little as 2 days' supply may be fatal. Furthermore, acute use may unintentionally turn into chronic use, in which case larger quantities will be prescribed.

II (2.2) Educational campaign

This measure has previously been considered by CSM and is discussed again in section 6 above.

II (3) DISCUSSION OF MAH APPEAL

There has been no conclusive research with repeat dosing of co-proxamol. The crux of the MAHs' argument for efficacy in chronic use is that acute dosing studies (none of which show efficacy superior to full strength paracetamol) are not relevant to chronic use as dextropropoxyphene accumulates with repeat dosing. The MAH's proposed restriction of indications to second-line use is not clearly defined and there is no evidence base to support. Arguments in favour of acute use are marked by their absence but the MAH's do not appear to consider dropping this indication.

If co-proxamol is to remain available for any amount of time, optimised product information and education would be of vital importance. The MAHs have made a good start with proposed changes to the product information but these require further amendment and retesting using a more appropriate interview-based methodology.

II (4) CONCLUSION REGARDING MAH APPEAL

The MAHs have used a wide range of information sources to address CSM's questions but are severely hampered by the absence of clinical trials conducted to modern standards of research, especially in chronic use. As the majority of co-proxamol usage is chronic (the MAH estimates that 65% of users have been taking it for >2 years), proposals to restrict indications to second line use are unlikely to have a major impact on the size of the population at risk of fatal toxicity.

The MAHs have demonstrated that there is room for improvement regarding warnings in the product information and this may enhance safety but the proposed availability of a smaller pack size is unlikely to have a significant effect as most use is chronic.

The Committee may consider that points 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8 and 2.9 of the CSM letter dated 4 June 2004 have not been addressed satisfactorily.

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.

There is no support for acute use and the MAHs have not attempted to specifically defend this indication. 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. The MAHs have made a good start with proposed changes to the product information but these require further amendment and retesting using a more appropriate interview-based methodology.

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 question is whether the MAHs' proposed measures to improve safety would reduce the risk of accidental toxicity and reduce the risk of fatal self-poisoning.

The MAHs' proposals for SPC amendment restricting indications to second line use, and for the availability of a smaller pack size are not aimed at significantly reducing usage and may therefore be unlikely to have a significant impact.

The CSM is asked to consider whether the MAHs have addressed satisfactorily the concerns raised in the 'minded to revoke' letter, as informed by the responses to the public consultation. 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.

11 ADVICE SOUGHT

The Committee is asked to consider whether the MAHs have satisfactorily answered all of the points raised by CSM in their letter of 4 June 2004, and to advise on any necessary regulatory action to address the risk:benefit of co-proxamol and appropriate measures to improve safety.

[redacted]

October 2004

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Annex 1

COMMITTEE ON SAFETY
OF MEDICINES

RESTRICTED - COMMERCIAL

The Company Secretary
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4th June 2004

Dear Sir/Madam,

Re: Distalgesic (Co-Proxamol Tablets) PL 19477/0011

1. The Committee on Safety of Medicines, having considered the available evidence, is minded to advise the Licensing Authority to exercise its powers under regulation 6(1) of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 to revoke the Marketing Authorisations listed above, on the basis that these products have proved harmful under normal conditions of use, and that therapeutic efficacy is lacking in the management of mild to moderate pain.

2. The reasons for the proposal are as follows.

Safety

2.1 Co-proxamol in overdose has been shown to be highly toxic and a proportion of deaths (approximately one fifth) are classified as accidental. While there is variability in the range and estimates of fatal co-proxamol doses, as few as 6 co-proxamol tablets have been considered sufficient to cause a fatal outcome.

2.2 There are additive toxic effects when co-proxamol is taken with alcohol and / or other central nervous system depressants.

2.3 Dextropropoxyphene may be cardiotoxic due to sodium channel blockade and prolongation of the QRS interval, resulting in cardiac arrhythmia.

2.4 The current warnings and advice to health professionals on the use of co-proxamol, strengthened in 1985, have not been shown to be effective in preventing adverse effects, including fatalities associated with co-proxamol.

Efficacy

2.5 There is no robust evidence to support the efficacy of co-proxamol in the management of chronic pain syndromes.

2.6 There is no robust evidence for synergy of paracetamol with dextropropoxyphene, and therefore its rationale as a fixed combination product requires to be supported.

2.7 The evidence from acute dose studies is that co-proxamol has not been shown to be more effective than paracetamol 650mg or 1000mg alone.

Risk:benefit

2.8 Having regard to the available efficacy and safety data, the benefits associated with co-proxamol in the authorised indications can no longer be considered to outweigh the risks.

2.9 The Committee does not consider that the balance of risks and benefits could be made favourable by restricting use to particular populations or indications. In particular, there is no evidence to support restriction of the indications to patients intolerant of, or unresponsive to, other drugs.

3. In accordance with paragraph 6(2) of Schedule 2 to the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994, before the Licensing Authority proceeds further with the proposal, you are offered the opportunity to make written or oral representations to the Committee on Safety of Medicines, provided that you give notice to the Committee that you wish to do so within one month of the date of this notice.

4. If you indicate that you wish to make oral representations, a hearing will be arranged for you. Provisionally, this will be 10 November 2004. A pre-hearing is provisionally booked for 13 October 2004. If you wish the Committee to consider written material at that meeting, 25 copies of any such material must be submitted to the Committee by 1 September 2004. The material should be as concise as possible and directly relevant to the reasons for the proposal referred to above.

5. If you do not wish to have an oral hearing but wish to make written representations to the Committee, these must be submitted to the Committee by 1 September 2004. Again, the material should be as concise as possible and directly relevant to the reasons for the proposal referred to above.

6. A copy of the assessment report will be provided to you in strict confidence to afford you an opportunity to respond as fully as possible to the points the Committee has raised. Disclosure of the report by you to a third party, unless in performance of a duty, could be an offence under section 118 of the Medicines Act 1968.

7. As marketing authorisations for co-proxamol exist elsewhere in the European Community, you may be able to refer the matter to the Committee for Medicinal Products for Human Use under article 31 of Directive 2001/83/EC. We would be grateful if you could notify us if this is your intention.

8. Please acknowledge receipt of this letter. I look forward to receiving an early reply advising me of your intentions.

Yours faithfully

[redacted]

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Annex 2