Letters first released with FOI 09 147

Dear [redacted]

Thank you for your email about the withdrawal of the pain killer co-proxamol.

I am sorry that the withdrawal of co-proxamol is causing concern and inconvenience to some patients who, like your mother, have been taking co-proxamol without experiencing any problems and do not consider themselves to be at risk of deliberate or accidental overdose. This was not an easy decision to make and follows an extensive risk:benefit assessment, a wide consultation and advice from the Committee on Safety of Medicines (CSM) – the Government's former independent scientific advisory committee on medicine safety (now the Commission on Human Medicines) - and other experts.

We recognise that there is a small group of patients who are finding it very difficult to change from co-proxamol and for these patients there is a provision for the supply of unlicensed co-proxamol, on the NHS. This is not an unusual arrangement and medicines may be supplied on this basis, but the responsibility for deciding whether or not to make use of that provision lies with the prescriber. The risks and benefits of the continued supply of an unlicensed medicine for individual patients must be weighed up by the prescriber in consultation with the patient.

I understand from your email that your GP is not willing to prescribe unlicensed co-proxamol in this way. Another doctor may be able to help and your mother may wish to seek a second opinion. For example there may be a possibility of provision through a pain clinic at your mother's local hospital, and her GP would need to authorise a referral.

The decision to withdraw co-proxamol from the market has tested medicines regulation to the extreme. Weighed against the difficulty for individual users is the clear public health gain from the removal of a medicine which has been widely implicated in accidental and non accidental overdose. Sometimes regulation has to balance the needs of the individual against the benefits at a population level. In this case the removal of marketing authorisations with continued use possible in exceptional circumstances is the best balance that could be achieved.

Yours sincerely

co-proxamol

Dear sir or madam,

I understand that Co-proxamol has been withdrawn due to safety concerns. I am writing on behalf of my 79 year old mother who has been using this drug for many years for widespread pain caused variously by arthritis, sciatica, failed hip-replacements and more recently following a diagnosis of breast cancer. My mother's G.P. will no longer prescribe Co-proxamol and no alternative drug has worked due to either an intolerance (caused by gullet and ulcer problems) or lack of strength of the painkiller, this includes Co-codamol.

Whilst I have read and understand the reasons for the withdrawal of the drug, I have been advised that there is provision for patients who are now struggling to manage chronic pain as a result of this decision, to still be prescribed Co-proxamol at the discretion of the G.P. "on the responsibility of the prescriber". Please can you respond with some more information/guidance on this possibility?

Many thanks

Yours faithfully

[redacted]

From: [redacted]
Sent: 07 July 2008 14:33
To: [redacted]
Cc: [redacted]
Subject: FOI - WITHDRAWAL OF COPROXIMAL FOI 08/253
Dear All

I don't know if you have seen the attached FOI as yet?
Grateful if you would confirm its receipt and process as appropriate.

Many thanks
[redacted]

From: [redacted]
Sent: 05 July 2008 11:02
To: [redacted]
Cc: [redacted]
Subject: WITHDRAWAL OF COPROXIMAL

THIS IS A FREEDOM OF INFORMATION ACT REQUEST

I am a patient whose withdrawal of Co-Proximal has had a huge impact on my life. I am writing to request copies of all letters and emails that you have received on the subject of Coproximal for the 18 month periods from 1st January 2007 to 30th June 2008.

I await this information with interest.

Many thanks,

[redacted]

Safeguarding public health

MHRA

[redacted]

25 July 2008

FOI 08/253

Dear [redacted]

Thank you for your Freedom of Information Act (FOIA) request of 5 July 2008 for all letters and emails that the MHRA have received relating to the withdrawal of Co-proxamol between 1 January 2007 and 30th June 2008.

The information you requested has already been released under FOI references 07/347, 08 017 and 08 242. The information already released covers letters received from 1 January 2006 to 30 June 2008 and replies from 1 December 2007 to 15 January 2008. Even though this goes beyond what you have requested, I am releasing all this information to you.

Information that could identify MHRA staff has been removed under Section 38 of the FOIA. Information that could identify other living individuals has been removed under Section 40 of the FOIA.

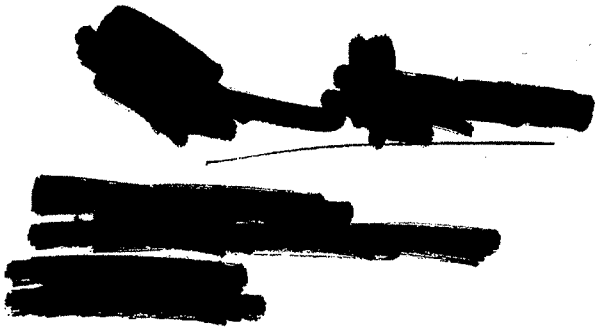
If you are unhappy with our decision to withhold certain information, you may ask for it to be reviewed. That review will be undertaken by a senior member of the Agency who has not previously been involved in your request. If you wish to pursue that option please write to the Communications Directorate, 10th Floor, Medicines and Healthcare products Regulatory Agency, at the above address quoting the reference number above. After that, if you remain dissatisfied, you may appeal to the Information Commissioner at:

The Information Commissioner's Office
Wycliffe House
Water Lane
Wilmslow.

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 **F** 020 7084 2353 www.mhra.gov.uk

I hope this information is of use to you.

Yours sincerely,



Enc

From: [redacted]
Sent: 11 July 2008 16:24
To: [redacted]
Cc: [redacted]
Subject: FOI 08/261 - FOI Website Request Thu Jul 10 17:19:00 BST 2008

Dear [redacted]

This is a Freedom of Information Request (Ref: FOI 08/261). The deadline for reply is 7th August 08.

Please see the FOI section on Insite for the SOP including templates to use for replies.

Pleaser remember to send copies of replies to [redacted] and [redacted]

Additionally please remember to use a copyright statement in your reply if data and documents are supplied. The FOI section on Insite contains wording on this.

Many thanks

[redacted]

-----Original Message-----
From: [redacted]
Sent: 10 July 2008 17:19
To: [redacted]
Subject: FOI 08/261 - FOI Website Request Thu Jul 10 17:19:00 BST 2008

Details of information required:
Dear Sir/Madam,
I am writing to submit the following request under the Freedom of Information Act:

1) Please indicate how letters and emails you have received on the subject of co-proxamol from January 2007 to July 2008.

2) How many were from GPs, specialists or patients?

3) Please send us copies of all letters and emails received on the subject of co-proxamol from this period.

In order to assist you with this request I am outlining my query as specifically as possible, but if this request is unclear then please contact me for clarification. I understand that under the Act I am entitled to a response within 20 working days.
I look forward to hearing from you.

Regards,

[redacted]

[redacted]

Mobile:

[redacted]

[redacted]

Safeguarding public health

MHRA

[redacted]

25 July 2008

FOI 08/261

Dear [redacted]

Thank you for your Freedom of Information Act (FOIA) request of 10 July about letters and emails that the MHRA have received relating to the withdrawal of Co-proxamol between 1 January 2007 and 30th June 2008.

The information you requested has already been released under FOI references 07/347, 08 017 and 08 242. The information already released covers letters received from 1 January 2006 to 30 June 2008 and replies from 1 December 2007 to 15 January 2008. Even though this goes beyond what you have requested, I am releasing all this information to you.

Letters received 1 January 2006 to June 2008 can be broken down as follows:

GP/Specialist	*5*
Patients/carers	*73*
Other health professional	*17*
MPs on behalf of patients	*86*
Other/not stated	*17*
Total	*198*

Information that could identify MHRA staff has been removed under Section 38 of the FOIA. Information that could identify other living individuals has been removed under Section 40 of the FOIA.

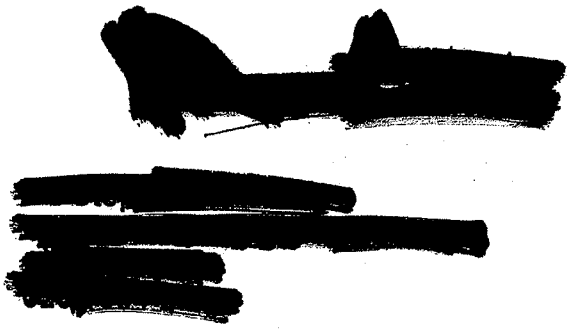
Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

If you are unhappy with our decision to withhold certain information, you may ask for it to be reviewed. That review will be undertaken by a senior member of the Agency who has not previously been involved in your request. If you wish to pursue that option please write to the Communications Directorate, 10th Floor, Medicines and Healthcare products Regulatory Agency, at the above address quoting the reference number above. After that, if you remain dissatisfied, you may appeal to the Information Commissioner at:

The Information Commissioner's Office
Wycliffe House
Water Lane
Wilmslow.

I hope this information is of use to you.

Yours sincerely,



Enc

From the Rt Hon Dawn Primarolo MP
Minister of State

DH Department of Health

Richmond House
79 Whitehall
London
SW1A 2NS

Tel: 020 7210 3000

PO00000332822

[redacted]
House of Commons
Westminster
London SW1A 0AA

Dear [redacted]

07 AUG 2008

Thank you for your further letter of 16 July enclosing correspondence from your constituent [redacted] about the withdrawal of the painkiller co-proxamol.

As you know, co-proxamol was withdrawn from the market at the end of 2007 by the Medicines and Healthcare Products Regulatory Agency (MHRA) on safety grounds. However, MHRA recognised that there is a small group of patients who found it difficult to change from co-proxamol, and for these patients there is a provision for the supply of unlicensed co-proxamol on the NHS, on the responsibility of the prescriber on a 'named patient' basis.

'Named patient' basis prescribing allows a prescriber to prescribe an unlicensed drug to a particular 'named patient'. As I said in my previous response, supplying drugs in this way is not an unusual arrangement, but the responsibility for deciding whether to do so or not lies with the prescriber. The risks and benefits of the continued supply of an unlicensed medicine for individual patients must be weighed up by the prescriber in consultation with the patient.

Such decisions are best left to healthcare professionals. If [redacted] still has concerns about his wife's pain relief, he and his wife should discuss them further with his wife's GP.

I hope this reply clarifies the Government's position.

Yours ever,

Dawn

DAWN PRIMAROLO

[redacted] M.P.

House of Commons
London, SW1A 0AA

[redacted] (Private Office - a.m. only)
[redacted] (FAX - 24hr)
020 7219 [redacted] (House of Commons)
020 7219 [redacted] (Members' messages)
website [redacted]

16/07/2008

The Rt Hon Dawn Primarolo MP
Minister of State
Department of Health
Richmond House
79 Whitehall
LONDON SW1A 2NS

Your ref: PO0000307813

Dear Dawn

Co-proxamol [redacted]

Further to our correspondence and your letter of the 26 May I would welcome clarification of the precise position: In your letter you say that "we have withdrawn Co-proxamol from the market".

In an email sent to [redacted] dated the 11 July [redacted] states that "Co-proxamol remains available on a named patient basis" and would appear to suggest that therefore [redacted] General Practitioner may continue to prescribe Co-proxamol if in his clinical judgement that is desirable.

Which is correct?

With my best wishes.
Yours [redacted]

[redacted]

Cc [redacted]

[redacted]

From: [redacted]
To:
Cc:
Sent: 11 July 2008 10:46
Subject: RE: Co Proxamol

Dear [redacted]

Thankyou for your e-mail

As you can imagine journalists take such comments out of context.

The reason why co-proxamol remains available on a "named patient" basis, and thus available to patients such as your wife if deemed clinically indicated by her physicians is because of the situation you describe.

Removal of this drug from the general list of products prescribed has saved a significant number of lives already. If enacted 20 years ago we estimate over 2000 patients who died would still be alive. At the present time we estimate about 200 lives a year are being saved.

This may place my views in perspective. I care for many young adults who have died from impulsive actions by taking their relatives pills.

I am sorry to hear of your wifes distress,

Yours sincerely

[redacted]

TOXBASE: http://www.Toxbase.org

-----Original Message-----
From: [redacted]
Sent: 11 July 2008 08:23
To: [redacted]
Cc: dhmail@dh.gsi.gov.uk; [redacted]
Subject: Co Proxamol

[redacted]

Having read your quote in Pulse,

" He said he had wanted to see co-proxamol phased out decades ago: 'I don't want to minimise the problem of controlling pain in general practice but the drug was never that good - addictive

but never that good."

Can I say that such a sweeping statement offends me, you have not asked my wife who had taken this drug for numerous years and was the only drug apart from Morphine that reliefs the daily pain that she is in, all you see are statistics (My wife is not a number).

Due to the actions of so called experts and the government my wife is daily in pain.

Thank You

[redacted]

Normal bloke with no letters after his name.!

CC Dawn Primarolo

[redacted]

Safeguarding public health

MHRA

30 July 2008

[redacted] MP
[redacted]

Dear [redacted]

Thank you for your letter about your constituent [redacted] and the withdrawal of the pain killer co-proxamol, and for enclosing a response to our review of the regulatory arrangements in place concerning unlicensed medicines.

I am sorry that the withdrawal of co-proxamol is causing concern and inconvenience to some patients who, like your constituent, have been taking co-proxamol without experiencing any problems and do not consider themselves to be at risk of deliberate or accidental overdose. This was not an easy decision to make and follows an extensive risk:benefit assessment, a wide consultation and advice from the Committee on Safety of Medicines (CSM) – the Government's former independent scientific advisory committee on medicine safety (now the Commission on Human Medicines) - and other experts.

The problem with co-proxamol (a combination of the weak opiate painkiller dextropropoxyphene with a relatively low dose of paracetamol) is two-fold; its dextropropoxyphene component is extremely hazardous in overdose and there is little, if any, evidence that it offers an advantage over full strength paracetamol. Co-proxamol has been involved in 300-400 self-poisoning deaths each year, of which around a fifth were accidental. Many deaths involved people taking co-proxamol that had not been prescribed to them. Co-proxamol can be very toxic, and overdose can occur with only a few tablets more than the recommended daily dose. Death from co-proxamol overdose is extremely rapid compared with other pain relieving medicines so that victims often die before they reach hospital. Whilst the dangers of co-proxamol are well-established, there is very little objective evidence that co-proxamol is any more effective in treating pain than normal paracetamol in the recommended dose. Furthermore, paracetamol is considered to have a comparatively good safety profile; onset of toxic effects is slow, allowing more time for rescue and a larger quantity of tablets is required to cause serious harm.

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

During 2004, the CSM comprehensively reviewed all the available evidence regarding the risks and benefits of co-proxamol. A public call for evidence on the risks and benefits of co-proxamol was also conducted for 12 weeks in 2004; the Medicines and Healthcare products Regulatory Agency (MHRA) wrote directly to a large number of organisations representing healthcare professionals, patient groups and other stakeholders as well as publishing the request for information on the MHRA website (www.mhra.gov.uk). Comments from patients and members of the public, as well as healthcare professionals were welcomed. Unfortunately the information gathered during this exercise provided no new objective evidence concerning the risk:benefit of co-proxamol.

The CSM noted that previously strengthened warnings to doctors and patients on the hazards of co-proxamol had proved ineffective. After considering the wide range of available evidence and the options for action to reduce the risk of overdose (e.g. prescriber and patient education, smaller pack sizes and restricted indications) the CSM determined that the risks of co-proxamol clearly outweigh the benefits of allowing the medicine to remain on the market.

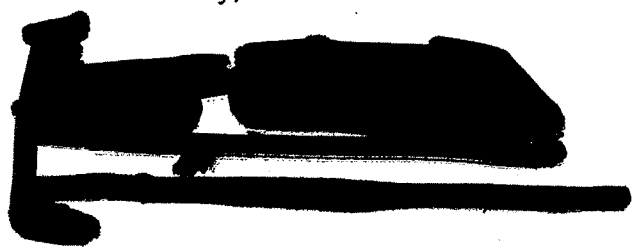
We recognise that there is a small group of patients who are finding it very difficult to change from co-proxamol and for these patients there is a provision for the supply of unlicensed co-proxamol, on the responsibility of the prescriber, as has been considered for your constituent. This is not an unusual arrangement and medicines may be supplied on this basis, but the responsibility for deciding whether or not to make use of that provision lies with the prescriber. I note, however, that your constituent's GP and consultant have said that their medical defence organisations would not cover them if they prescribed unlicensed co-proxamol. Medical defence organisations offer their members a range of services which may include professional indemnity insurance. The organisations are, however, independent of Government and therefore the MHRA cannot comment on the cover provided for GPs when they prescribe an unlicensed medicine.

The current regulatory provisions which allow an authorised healthcare professional to commission an unlicensed medicinal product to meet the special needs of an individual patient have been in place for a number of years. Given the developments that have taken place over the years there is now a clear case for reviewing those provisions. The period of informal consultation with a range of stakeholders has just completed and we are considering the responses received. We envisage it is likely that a formal consultation exercise will take place later in the year setting out specific proposals for reform of the current arrangements.

from the removal of a medicine which has been widely implicated in accidental and non accidental overdose. Sometimes regulation has to balance the needs of the individual against the benefits at a population level. In this case the removal of marketing authorisations with continued use possible in exceptional circumstances is the best balance that could be achieved.

It is encouraging to see that a recent report from the national programme on substance Abuse Deaths (np-SAD) based at St George's Hospital in London, shows that the number of deaths involving co-proxamol has declined since the CSM took action.

Yours sincerely,



[redacted]

[redacted]

HOUSE OF COMMONS
LONDON SW1A 0AA

Please reply to:
[redacted]

11 July 2008

[redacted]

Dear [redacted]

Re [redacted] and co-proxamol

I have enclosed a copy of a submission that my constituents, [redacted] sent to you recently.

[redacted] is in pain and it appears that taking co-proxamol tablets is the only way that she can get relief from the pain.

I am very sympathetic to [redacted] predicament and would be grateful if you would study the enclosed submission and respond to me.

Yours sincerely

[redacted]

Enc

MHRA
16 JUL 2008
DIRECTORATE
11986

1. Log + Ack.
16 JUL 2008 [redacted]

2. B/F 7 days

cc [redacted]

Whilst [redacted] will treat as confidential any personal information which you pass on, he will allow staff and authorised volunteers to see it if this is needed to help and advise you. The MP may pass all or some of the information to agencies, such as DSS, Inland Revenue or Local Council if this is necessary to help with your case. We may wish to write to you, from time to time, to keep you informed on issues that you might find of interest. Please let him know if you do not wish to be contacted for this purpose.

[redacted]

[redacted]

From: [redacted]
Sent: 30 June 2008 22:28
To: [redacted]
Subject: FW: Informal consultation paper on the review of the regulation of unlicensed medicines

From: [redacted]
Sent: 30 June 2008 08:19
To: [redacted]
Cc: [redacted]
Subject: Informal consultation paper on the review of the regulation of unlicensed medicines

Dear [redacted]

Please accept this submission on behalf of [redacted] regarding the use and prescribing of certain unlicensed medicines. I am full time carer to [redacted]. Although it refers to one particular patient and one particular drug, I believe that the general principles for review and consultation are affected by the issues it throws up, so I respectfully request that it be included as a valid submission.

---

1) Overview

My wife was prescribed Co-proxamol tablets (Propoxyphene and Paracetamol) for many years until 18 months ago when they were suddenly stopped without explanation.

Further enquiries to the GP surgery only got the answer that "they had been withdrawn".

Feeling that she should still get this drug as that it was effective and was one of the few that did not cause any side effects, enquiries were made of the GP about Pain Clinics prescribing this particular drug .

Appointments with a Pain Clinic and Consultant were made and the consultant there decided that other alternatives would not be as effective as Co-proxamol and recommended to her GP in writing that Co-proxamol should be prescribed.

2) Prescriptions

Her GP then wrote a prescription earlier this year which was fulfilled by the local pharmacy. The pharmacy identified that Co-proxamol was discontinued and obtained my wife about 2 years supply until alternatives could be identified.

3) Legal position of GPs

Then, my wife received a letter from her GP stating that the GPs Medical Defence Union would not cover her if she prescribed Co-proxamol.

Enquiries to the Consultant (who contacted her managers in [redacted] to find out) revealed a similar story, her MDU would also not cover her if she prescribed CP.

4) Availability of Propoxyphene

In the course of discussions with the Consultant it was stated by the consultant's Registrar that Propoxyphene was available as Darvocet over the internet.

This appears now to be the only way patients such as my wife can now obtain this drug. This is far from ideal, because not only might drugs be seized by Customs, they are also sold at "street value" currently I am led to believe, about 50p per tablet.

5) Details of the effectiveness of Propoxyphene

I would like to point out certain things that have come to light in the course of trying to ensure my wife has proper pain relief.

The main objection to this drug seems to have been made by pressure groups campainging on the premis that its a dangerous drug, ie it is implied in some cases of suicide/euthanasia. My wife has never been identified as at risk or in a patient group that would be at risk from taking an overdose. She has many other much more dangerous drugs on prescription regularly.

i) The studies that I have identified only refer to Propoxyphene's effectiveness in Post-operative pain relief and NOT in Fybromyalgia and Soft Tissue Rheumatism which is mainly what my wife's pain comprises. If they had asked FMS/ME/CFS sufferers about the effectiveness of CP there would be revealed a rather different conclusion I feel.

ii) The studies quoted identify alternatives to CP, eg Tramadol and Codeine but fail to note the problems associated with these drugs like severe constipation and/or vomiting, which is clinically a very significant factor for patients such as my wife who already takes many other strong medications that cause side effects. Codeine is also highly addictive.

iii) Pain is a very subjective thing, each person experiences and tolerates it differently, but the relief that my wife gets from this one medication is very significant and cannot be replicated with other medicines which have been tried

from prescriptions and letters sent directly to us to inform us of any consultations. If such a system were in place I feel sure that the people thus affected would have had a voice and would have objected more loudly had they know of its imminent withdrawal.

Even if medicines are withdrawn there should still be a system by which the NHS can prescribe drugs (if they are shown to be effective for particular patients) and doctors can remain covered by their defence unions.

Please accept this short submission as part of your review as I feel sure that my wife's story is not unique and that it may add something to the discussion as I feel sure that she and many other patients "fall through the gaps" in the system as it is.

I realise the deadline was today, but I have only just seen this as a result of publicy about other drug precibing issues "postcode lottery" etc.

Many thanks

Kind regards

[redacted]

Dated 30/06/08 08:06 AM

[redacted]

01/07/2008

ICR 897

[redacted]

19th July 2008

MRHA
10-2 Market Towers
1 Nine Elms Lane
London
SW8 5NQ

Dear Sir or Madam

RE: Withdrawal of Co-Proxamol

I am writing to you as one of the long suffering arthritis patients who were prescribed the drug Co-Proxamol and one of the individuals from whom this drug has now been withdrawn.

The withdrawal of this drug in December 2007 has affected many people who, like myself, cannot physically function without it. I have been prescribed alternatives as I am unable to take anti-inflammatory medication due to a stomach ulcer I had some years ago. Tramadol made me feel like a zombie; Co-Dydromal and Co-Codamol cause me to feel violently sick along with making me constipated, so much so that this in turn leads to bleeding haemorrhoids.

If the reason for withdrawal of this drug was due to the suicides that have been reported I would like to point out that not all users of this medication misuse it, nor consume alcohol whilst taking it. Paracetamol can be just as effective if someone wishes to end their life but as regards relief of my pain this does nothing for me.

After two doses (2 x 2 tablets) of Co-Proxamol I am able to function again as an active human being and not a shrivelled up old woman – I have only just turned 65 years of age - to be condemned to feeling like this due to the withdrawal of this drug is very upsetting. To not be able to have the medication that helps you when you are suffering is inhumane.

I am not afraid to take this issue to the media on behalf of myself and all other arthritis sufferers who are unable to take other forms of medication for their pain. If you conducted market research you would find that for some individuals, like myself, Co-Proxamol is the only thing we can take that agrees with us and does not give us unpleasant and unacceptable side effects. You

only have to look at websites such as the arthritis charity, Arthritis Care, to see that this is indeed the case.

It is my understanding that the Government now want patients to tell their GP what works for them. I personally see no point in being asked to do this when the medication is not available. I also understand that doctors are now afraid to prescribe this medication because if anything goes wrong they will be held responsible. If it was written in black and white that this drug is the only one that is suitable for a given patient and that patient signed a disclaimer to this effect then surely the responsibility would then end with the patient not the GP?

I hope that these tablets can be reinstated to those who have no suicidal tendencies and do not drink as the majority, in my opinion, are suffering for the reckless few. I want this not just for my own sake but also for the well-being of others like me who cannot take the other types of medication available.

I would ask you to please think again about the people who are in pain and suffering because of the removal of this medication from the market. I believe you have had a lot of enquiries about this matter already.

Yours faithfully

[redacted]

[redacted]

cc. [redacted]

Safeguarding public health

MHRA

[redacted]

[redacted]

24 July 2008

Dear [redacted]

Thank you for your letter dated 19 July 2008 about the withdrawal of the pain killer co-proxamol. I am sorry that the withdrawal of co-proxamol is causing concern and inconvenience to some patients who, like you, have been taking co-proxamol without experiencing any problems and do not consider themselves to be at risk of deliberate or accidental overdose. This was not an easy decision to make and follows an extensive risk:benefit assessment, a wide consultation and advice from the Committee on Safety of Medicines (CSM) – the Government's former independent scientific advisory committee on medicine safety (now the Commission on Human Medicines) - and other experts.

The problem with co-proxamol (a combination of the weak opiate painkiller dextropropoxyphene with a relatively low dose of paracetamol) is two-fold; its dextropropoxyphene component is extremely hazardous in overdose and there is little, if any, evidence that it offers an advantage over full strength paracetamol. Co-proxamol is involved in 300-400 self-poisoning deaths each year, of which around a fifth are accidental. Many deaths involve people taking co-proxamol that had not been prescribed to them. Co-proxamol can be very toxic, and overdose can occur with only a few tablets more than the recommended daily dose. Death from co-proxamol overdose is extremely rapid compared with other pain relieving medicines so that victims often die before they reach hospital. Unlike paracetamol, there is no effective 'antidote' to co-proxamol poisoning. Whilst the dangers of co-proxamol are well-established, there is very little objective evidence that co-proxamol is any more effective in treating pain than normal paracetamol in the recommended dose. Furthermore, paracetamol is considered to have a comparatively good safety profile; onset of toxic effects is slow, allowing more time for rescue and a larger quantity of tablets is required to cause serious harm.

[redacted]

The CSM noted that previously strengthened warnings to doctors and patients on the hazards of co-proxamol had proved ineffective. After considering the wide range of available evidence and the options for action to reduce the risk of overdose (e.g. prescriber and patient education, smaller pack sizes and restricted indications) the CSM determined that the risks of co-proxamol clearly outweigh the benefits of allowing the medicine to remain on the market.

We recognise that there is a small group of patients who are finding it very difficult to change from co-proxamol and for these patients there is a provision for the supply of unlicensed co-proxamol, on the responsibility of the prescriber. This is not an unusual arrangement and medicines may be supplied on this basis, but the responsibility for deciding whether or not to make use of that provision lies with the prescriber. The risks and benefits of the continued supply of an unlicensed medicine for individual patients must be weighed up by the prescriber in consultation with the patient. The MHRA has sought legal advice on the possibility of a consent form to transfer the responsibility from the prescriber to the patient. The legal advice was that if unlicensed co-proxamol is prescribed, the doctor must take direct personal responsibility for this. A patient disclaimer/consent form cannot remove or satisfy that requirement as a doctor still has a responsibility to exercise his or her clinical judgment as well as a separate legal obligation to obtain informed consent to any treatment.

It is encouraging to see that a recent report from the national programme on substance Abuse Deaths (np-SAD) based at [redacted] in London, shows that the number of deaths involving co-proxamol has declined since the CSM took action.

The decision to withdraw co-proxamol from the market has tested medicines regulation to the extreme. Weighed against the difficulty for individual users is the clear public health gain from the removal of a medicine which has been widely implicated in accidental and non accidental overdose. Sometimes regulation has to balance the needs of the individual against the benefits at a population level. In this case the removal of marketing authorisations with continued use possible in exceptional circumstances is the best balance that could be achieved.

Yours sincerely

[redacted]

[redacted]

From: [redacted]
Sent: 30 July 2008 16:12
To: [redacted]
Subject: FW: Co-proxamol - Ref DE286914

Dear [redacted]

Thank you for your email of 27 July 2008 about the withdrawal of co-proxamol.

Unfortunately the Medicines and Healthcare products Regulatory Agency (MHRA) has no direct responsibility for provision of healthcare and so cannot advise individual patients on how to manage their own healthcare, although as previously suggested another doctor might be able to help you. Alternatively you might wish to contact your local [redacted]

I am sorry but there is no further advice I can give you on this matter .

Yours sincerely

[redacted]

From: [redacted]
Sent: 27 July 2008 11:34
To: [redacted]
Subject: RE: Co-proxamol - Ref DE286914

You suggested I sought a second opinion in your email to me of the 11th of March 2008 and I have described to you the circus of delays and evasions which subsequently took place resulting in a second refusal to prescribe a few weeks ago.

I remind you that the DoH position is that co-proxamol is still available for those for whom there is no effective substitute. This is working for some post codes.
I beseech you to explain how it can be made to work in PO16. My whole quality of life is now collapsing and my GP and I cannot determine the cause because **I am unable return to the status quo before collapse.**

I presume you are advising me to obtain a third opinion. Should I try [redacted], for example?

[redacted]

From: [redacted]
Sent: 18 July 2008 11:41
To: [redacted]
Subject: FW: Co-proxamol - Ref DE286914

Dear [redacted]

Thank you for your email about co-proxamol. I am sorry for the delay in responding, however, I have been out of the office for the last few weeks. I am also sorry that the withdrawal of co-proxamol is still causing you concern and inconvenience.

I note that your GP is not prepared to continue to prescribe unlicensed co-proxamol despite the letter from the pain clinic.

Unfortunately the only way to receive unlicensed co-proxamol is via a prescription and only a prescriber, in consultation with the patient, can make the judgement about the appropriate pain management regime for that patient.
As you point out, other doctors are continuing to prescribe co-proxamol. As previously suggested, another doctor may be able to help and you may wish to seek a second opinion.

Yours sincerely

[redacted]

From: [redacted]
Sent: 08 July 2008 21:11
To: [redacted]
Subject: RE: Co-proxamol - Ref DE286914

I am replying again to this old email to describe subsequent events and their futility.

At your suggestion, I saw my GP again and asked for a second opinion by referral to the local hospital [redacted]
After several weeks I saw [redacted] in the [redacted]. He prescribed Tramadol but took on
board my request to be returned to co-proxamol. 10 weeks went by during which I expedited action via the secretary each
week. On opening the Tramadol I had found the package leaflet which stated Tramadol is counter-indicated if there
is risk of fits. I am diabetic on Insulin (a fact I made clear to [redacted] and have to be vigilant to avoid hypo fits so clearly
it was not for me. After 10 weeks [redacted] wrote to my GP asking him to prescribe co-proxamol. Meanwhile, the local practice
had forbidden all non-licenced prescribing because of medical insurance invalidation considerations and have not even bothered to reply
to the [redacted] equest letter. So, after months of patient waiting, and following your and others' advice **I am no nearer to
realising the provision in law** to which you refer below.

In colloquial terms, I have been given the run-around.

I understand from a relevant internet thread (http://www.dummies-for-destruction.co.uk/random/index.php/?p=2366) that several
postcodes are now back prescribing co-proxamol to the needy despite the price-hike.

Can you please, urgently, suggest my next move since my Quality of Life is now collapsing, - disablement, - cancelled holidays,
threats to limbs, due to pain inhibiting regular exercise

From: [redacted]
Sent: 11 March 2008 16:38
To: [redacted]
Subject: Co-proxamol - Ref DE286914

Dear [redacted]

Thank you for your email about the withdrawal of co-proxamol. As the Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for medicines regulation I have been asked to reply.

May I start by saying that I am sorry that the withdrawal of co-proxamol is causing you concern and inconvenience.

As stated in previous correspondence, for patients who are finding it difficult to change to an alternative to co-proxamol, for example when alternatives appear not to be effective or suitable, there is a provision in law for the supply of unlicensed co-proxamol on the NHS. This is not an unusual arrangement and medicines may be supplied on this basis, but the responsibility for deciding whether or not to make use of that provision lies with the prescriber. The risks and benefits of the continued supply of an unlicensed medicine for individual patients must be weighed up by the prescriber in consultation with the patient.

I understand from your email that your GP is not willing to prescribe unlicensed co-proxamol in this way. Another doctor may be able to help and you may wish to seek a second opinion. For example there may be a possibility of provision through a pain clinic at your local hospital, and your GP would need to authorise a referral.

The MHRA has sought legal advice on the possibility of a consent form to transfer the responsibility from the prescriber to the patient. The legal advice, which was reflected in Theo Raymond's response of 5 March, was that if unlicensed co-proxamol is prescribed, the doctor must take direct personal responsibility for this. A patient disclaimer/consent form cannot remove or satisfy that requirement as a doctor still has a responsibility to exercise his or her clinical judgment as well as a separate legal obligation to obtain informed consent to any treatment.

In order to try and support patients and doctors in finding suitable alternatives to co-proxamol, the Committee on Safety of Medicines - the Government's former independent scientific advisory group on medicines safety (now the Commission on Human Medicines (CHM) - established an Expert Working Group on Pain Management. The MHRA has already issued Pain Management guidance from this Committee to all prescribers. If your doctor remains unwilling to prescribe unlicensed co-proxamol, you may wish to further discuss alternative treatments or whether a referral is appropriate.

I hope you find this reply helpful.

Yours sincerely

[redacted]

From Ann Keen MP
Parliamentary Under Secretary of State

DH Department of Health

Richmond House
79 Whitehall
London
SW1A 2NS

Tel: 020 7210 3000

Your Ref: [redacted]

PO00000338195

[redacted]

Dear [redacted]

01 SEP 2008

Thank you for your letter of 1 August on behalf of a number of your constituents, in response to my letter to you of 28 February (our ref: PO00000280759) about the withdrawal of the painkiller co-proxamol. I am replying as duty Minister on behalf of Dawn Primarolo.

You ask if you could be provided with copies of any meeting notes that detail why the Chief Medical Officer (CMO) rejected the possibility of more prominent labelling. You also asked if you could be given a full explanation as to why more prominent labelling was not tried.

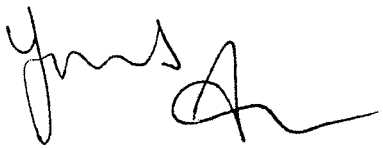
The Medicines and Healthcare products Regulatory Agency (MHRA) has attempted for years to lessen the risk of co-proxamol overdose by clearer labelling and information. Following the implementation of European Council Directive 92/27/EC, patient information leaflets were introduced for this product which set out clearly the need for patients to avoid alcohol whilst taking co-proxamol. At the same time clearer labelling was introduced which conveyed this message on the outer carton and on the blister foils of packaging. A further revision to the labelling was also instigated which brought together more safety information on the carton. Nevertheless, it was considered that the labelling information, whether applied alone or in combination with other safety measures, could not be relied upon to eliminate the risk of deliberate or accidental fatalities, hence the decision to phase out supply of this medicine.

A copy of the paper that was considered by the Committee on Safety of Medicines (CSM) together with the minutes of the meeting is enclosed. Some of the information was provided to the MHRA and the CSM in confidence and therefore where necessary the text has been redacted.

It is encouraging to see that the public health gain from the withdrawal of co-proxamol is already becoming apparent. A recent report from the National Programme on Substance Abuse Deaths based at St George's Hospital in London, shows that the number of deaths involving co-proxamol has declined since this action was taken.

Furthermore, a recent study using data from Scotland has shown that the withdrawal of co-proxamol has been accompanied by a significant reduction in the number of deaths from co-proxamol overdose in Scotland. The authors of the study have estimated that around 300 lives per annum in the UK will have been saved by the withdrawal of co-proxamol.

I hope this response is helpful.



ANN KEEN

[redacted] MP

HOUSE OF COMMONS

The Rt Hon Dawn Primarolo MP LONDON SW1A 0AA
Minister of State
Department of Health
Richmond House
79 Whitehall
LONDON
SW1A 2NL

1 August 2008
My Ref: [redacted]
Your Ref:
(Please quote our reference when replying)

DEPT OF HEALTH
RECEIVED
05 AUG 2008
CORRESPONDENCE
PRIVATE OFFICE CC

Dear Dawn

Co-Proxamol

Thank you for your letter of 28 February which I read with interest. Having discussed its contents with a number of constituents, some of them have asked why more consideration was not given to the possibility of more prominent labelling?

You state that the CSM did consider this and I would be grateful if you could provide copies of meeting notes and a full explanation as to why this measure was not tried.

I look forward to hearing from you.

Yours sincerely

[redacted]

[redacted] MP

Please reply to: [redacted]
Tel: [redacted] **Fax:** [redacted] **e mail** [redacted]

Papers

5. **Risk:Benefit of Co-proxamol Products**

5.1 [redacted] declared personal non specific interest in [redacted] and left the room. [redacted] declared a non personal non specific interset, but this did not debarr him from taking part in the proceedings.

5.2 The Committee noted **Tabled Papers II & IIa**

5.3 The Committee considered a review of the risk:benefit of co-proxamol (dextropropoxyphene and paracetamol) 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, in particular in overdose.

5.4 ONS death certification data for England and Wales between 1994 and 2001 showed that there were between 300 and 400 deaths per year where co-proxamol was mentioned and self-poisoning was the underlying cause of death. Around one-fifth of these were classified as accidental deaths and the rest as suicide or open verdict. A UK coroner's series of co-proxamol fatalities, published in 1981 showed that over 90% of deaths occurred outside hospital. On average 15 tablets were consumed but as few as 6 or 8 may have been associated with a fatal outcome.

5.5 An analysis of Office for National Statistics (ONS) data for England and Wales published in 2003 showed that in 1997-9 co-proxamol alone accounted for around 18% (~255 deaths per year) of fatal drug related self-poisonings in England and Wales classified as suicide or open verdict. Tricyclic antidepressants alone accounted for 22% of such fatalities (~309 deaths per year). Overdose with co-proxamol was twice as likely to be fatal as overdose with tricyclic antidepressants and 28 times as likely to be fatal than when paracetamol alone was taken in overdose. Analysis of 'definite' or 'probable suicides' in under 25-year-olds, in the Oxford region, published in 1999, showed that co-proxamol was the commonest agent used in self-poisoning and that the majority used co-proxamol prescribed for others.

5.6 The cardiotoxic effect of dextropropoxyphene due to prolongation of the QRS interval, sodium channel blockade and arrhythmias had also been documented and was highlighted in a UK publication in 2003. The non-specific membrane effects, which also cause CNS depression in acute overdose, were not reversible with opiate antagonists.

5.7 The Committee considered the evidence of efficacy of co-proxamol in the treatment of mild to moderate pain. Systematic reviews of randomised double blind trials of co-proxamol in acute pain did not show any additional benefit of co-proxamol over paracetamol 650mg. Single constituent dextropropoxyphene 65mg was not shown to be an effective analgesic.

5.8 The Committee considered the available efficacy studies of co-proxamol in chronic pain. Some of these studies provided limited information. The Committee considered that there was no robust evidence of efficacy in chronic pain syndromes.

5.9 The Committee concluded that risk:benefit balance of co-proxamol appeared to be unfavourable. The Committee deemed that there was insufficient evidence of efficacy to support restriction to cancer pain, neuropathic pain or chronic musculoskeletal conditions and that a wider range of pack sizes was unlikely to drive changes in prescribing practice.

5.10 The Committee noted that in 1985, its advice had been published, reinforcing strengthened warnings in the product information. The Committee noted that these warnings had not been effective in preventing deaths, including accidental deaths, associated with co-proxamol.

5.11 The Committee concluded that it was minded to advise that marketing authorisations for co-proxamol should be revoked. There should be 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 at the same time.

COMMITTEE ON SAFETY OF MEDICINES
SUBCOMMITTEE ON PHARMACOVIGILANCE
NOT FOR PUBLICATION

SCOP 2004/2nd
CSM 2004/8th

RESTRICTED - COMMERCIAL	**PL NUMBER:** Several
TITLE OF PAPER: RISK:BENEFIT OF CO-PROXAMOL PRODUCTS	
RISK: BENEFIT ASSESSMENT For advice	**THERAPEUTIC CLASSIFICATION:** Analgesic
LICENCE HOLDER: Several	**PRODUCT NAMES:** Co-proxamol Distalgesic
ACTIVE INGREDIENT: Dextropropoxyphene + paracetamol	**PREVIOUS CONSIDERATION BY CSM:** 1985
LEGAL STATUS: POM	**CONSIDERATION BY OTHER COMMITTEES:** None
SALE/SUPPLY: POM	

Index

EXECUTIVE SUMMARY

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

- Co-proxamol is indicated for '*mild to moderate pain*' with a usual maximum daily dose of 8 tablets. It contains paracetamol and dextropropoxyphene, a weak opioid analgesic that is known to be toxic in overdose; as few as 10-20 tablets may be fatal and death most often occurs within an hour, leaving little time for rescue. Co-ingestion of alcohol or other central nervous system depressants significantly increases risk.

- Each year 300-400 people in England and Wales commit suicide or fatally overdose with co-proxamol.

- There is growing concern prompted by recently published UK research showing that co-proxamol alone now accounts for almost one-fifth of drug-related suicides and is second only to tricyclic antidepressants as an agent of fatal drug overdose. In addition, concerns raised by Sweden in the European Parliament have prompted a referral to the Pharmacovigilance Working Party.

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

- Co-proxamol has not been subjected to modern standards of clinical research; there have been no robust studies of greater than 48 hours duration. It does not meet the European criteria for a 'fixed combination' product as there is no evidence of synergy between the active ingredients. A review of efficacy has shown that:-
  - For acute pain, there is no robust evidence that co-proxamol has superior analgesic efficacy to full strength paracetamol
  - For chronic pain (>48 hours), analgesic efficacy has not been demonstrated

- Prescribers have repeatedly been warned of the unproven efficacy and proven toxicity of co-proxamol for more than 20 years but it is still widely used by hospitals and is prescribed to approximately 1.7 million GP patients annually. (see section 6.1).

RISK:BENEFIT OF CO-PROXAMOL PRODUCTS

1 PROBLEM STATEMENT

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

2 INTRODUCTION

2.1 Fatal co-proxamol poisoning

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

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

2.2 History of co-proxamol/dextropropoxyphene

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

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

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

3 REGULATORY BACKGROUND

3.1 Licensing status

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

3.1.1 Indications

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

3.1.2 Posology

The usual daily dose of co-proxamol is 2 tablets three or four times per day in adults and the elderly.[2]

Use in children is not recommended

3.1.3 Pack size

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

Dextropropoxyphene napsylate is licensed in packs of 100 capsules only.

3.2 UK concerns

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

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

[1] February 2005 Update: There are currently 14 product licences for co-proxamol. Dextropropoxyphene is no longer marketed.

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

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

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

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

3.3 European Parliamentary Question (oral) of 21 May 2003

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

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

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

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

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

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

4 CLINICAL PHARMACOLOGY AND TOXICOLOGY

4.1 Clinical pharmacology

DXP is a synthetic opioid analgesic, with structural similarity to methadone. It binds primarily to μ-opioid receptors and produces analgesia and other CNS effects similar to those seen with morphine-like opioids. As an analgesic 90-120mg of DXP HCl administered orally would equal the analgesic effects of 60mg codeine[4] [5]. (NB a standard dose of co-proxamol contains only 65mg of dextropropoxyphene)
DXP is detectable in plasma 15-30 minutes after oral ingestion [6]. It is subject to extensive first pass metabolism in the liver and its main and active metabolite is norpropoxyphene (NXP), produced by N-demethylation. DXP is rapidly distributed and concentrated in the brain, liver, lungs and kidneys. Peak plasma concentrations occur within 1-2.5 hours of ingestion. Equimolar doses of DXP HCl and DXP napsylate produce similar plasma concentrations. After therapeutic doses plasma concentrations are in the range 0.05-0.75mg/l. In severe hepatic dysfunction, the plasma concentration of DXP is increased whilst that of NXP is reduced.

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

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

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[3] http://www.hmso.gov.uk/si/si2001/20013998.htm
[4] Goodman & Gilman's The Pharmacological Basis of Therapeutics, 2001,Tenth edition,

[5] Therapeutic drugs, 1999, Second edition, ed. Dollery, C. Publ. Churchill Livingstone, Edinburgh

[6] Drugs & Therapeutic Bulletin 21(5) (1983) 17-19.Distalgesic and its equivalents: Time for action

[7] Haigh, S. 34 (1996) 1840-1841 The Lancet 12 years on: co-proxamol Revisited

[8] PL 00006/5086R

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

4.2 Rationale for co-proxamol as a compound analgesic

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

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

4.3 Toxicity

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

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

4.3.1 Interaction of DXP with alcohol

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

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

Assessor's comment:
It is of great concern that avoidable accidental deaths may occur due to lack of awareness of the dangers of taking DXP with alcohol.

4.4 Dependence/Abuse

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

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

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

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

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

4.5 Current warnings in UK SPCs and Patient Information

4.5.1 Standard paracetamol warnings

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

Statutory labelling requirements

(products intended for use by adults and children over 12 years)

- The boxed warning

  Do not take with any other paracetamol-containing products

- The boxed warning

  Immediate medical advice should be sought in the event of an overdose, even if you feel well.

  (products with an accompanying leaflet) **or**

  Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage

  (if no accompanying leaflet)

Statutory leaflet requirement

(products intended for use by adults and children over 12 years)

- Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

4.5.2 SPCs

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

Alcohol
In 17 products the advice is to avoid alcohol and in the other, co-ingestion of alcohol with excessive doses of DXP is mentioned as one of the major causes of drug-related deaths.

CNS Depressants
All licences warn of the risk of concomitant use of CNS depressants to varying degrees. Some merely say that the effects may be additive to those effects of DXP whereas, some include the much stronger *"Excessive doses of DXP, either alone or in combination with depressants of the CNS (including alcohol) are a major cause of drug-related deaths. Fatal effects can occur within 15 minutes and are not uncommon within the first hour of overdosage. Some deaths have occurred as a result of excessive ingestion of [product] alone or in combination with other drugs."*

Mental illness, suicidality and addiction
Nine licences contain the contra-indication of patients who are suicidal or addiction-prone; four other licences contain the precaution of use in patients with a

psychological or personality disorder and one licence contains both statements.

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

4.5.3 Label

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

4.5.4 Patient Information Leaflets

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

Assessor's comment:

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

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

5 EVIDENCE OF EFFICACY

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

5.1 Acute pain

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

5.1 1 Acute moderate pain

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

5.1.2 Moderate-severe post-operative pain

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

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

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

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

5.2 Chronic pain

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

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

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

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

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

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

5.3 Reasons for the extensive use of co-proxamol

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

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

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

5.4 Treatment guidelines

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

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

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

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

[10] Goodman & Gilman's The Pharmacological Basis of Therapeutics, 2001,Tenth edition
[11] http://www.who.int/cancer/palliative/painladder/en/

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

5.5 Alternative analgesics

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

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

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

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

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

[12] BNF 46 September 2003 pp 210 and 212

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

Assessor's comment

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

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

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

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

5.6 Potential drawbacks of restricting co-proxamol usage

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

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

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

6 RISK ASSESSMENT

6.1 UK usage data

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

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

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

In summary:

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

6.1.1 Hospital dispensing (UK)

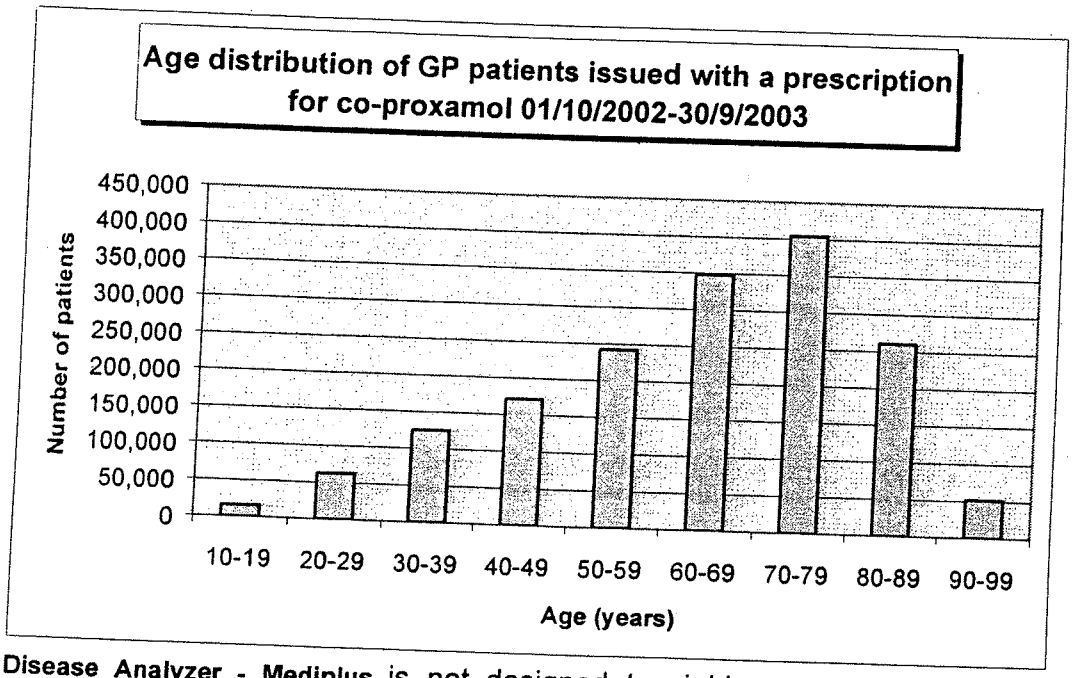
Hospital usage data were obtained for 1999-2002 for the whole of the UK. The data could not be split into subsets by age. These data are based on accurate information for 96% of the population which is then arithmetically corrected to account for the missing 4%. The fall in co-proxamol usage during this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

Table 1: hospital dispensing
The daily defined dose (DDD) of co-proxamol is 6 tablets or capsules and the DDD of paracetamol is 3g

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

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

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



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

These data have been obtained from the IMS Disease Analyzer - Mediplus database and the Hospital Pharmacy audit (HPA)

*The **Disease Analyzer - Mediplus database** contains anonymised computerised longitudinal records of patients' GP consultations and treatment. The practices are intended to be representative of the geographical distribution of GPs in the UK and the figures can be projected up to estimate UK numbers. The database contains the records of around 2.1million patients of which half are currently active.*

HPA data

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

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

6.1.3 Community pharmacy data 1995-2002 (England)

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

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

- Elderly (over 60 years)

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

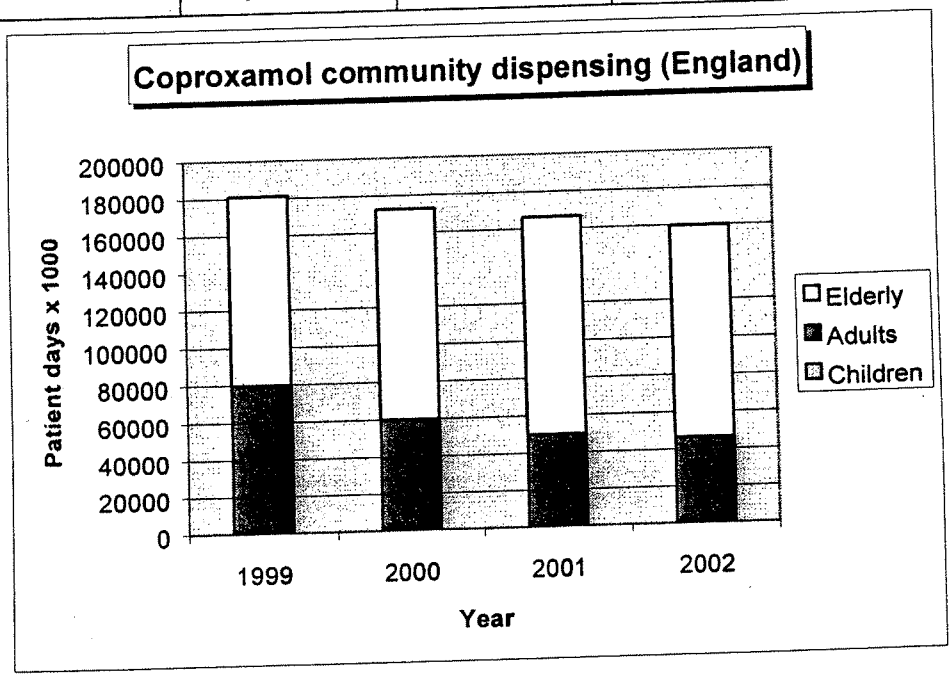


Figure 2: NB Single constituent DXP dispensing is 2000-fold lower and cannot be shown on the same chart. Use in children is also too small to be visible on this chart.

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

6.2 Mortality and morbidity

6.2.1 ONS Mortality data (England and Wales)

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

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

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

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

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

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

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

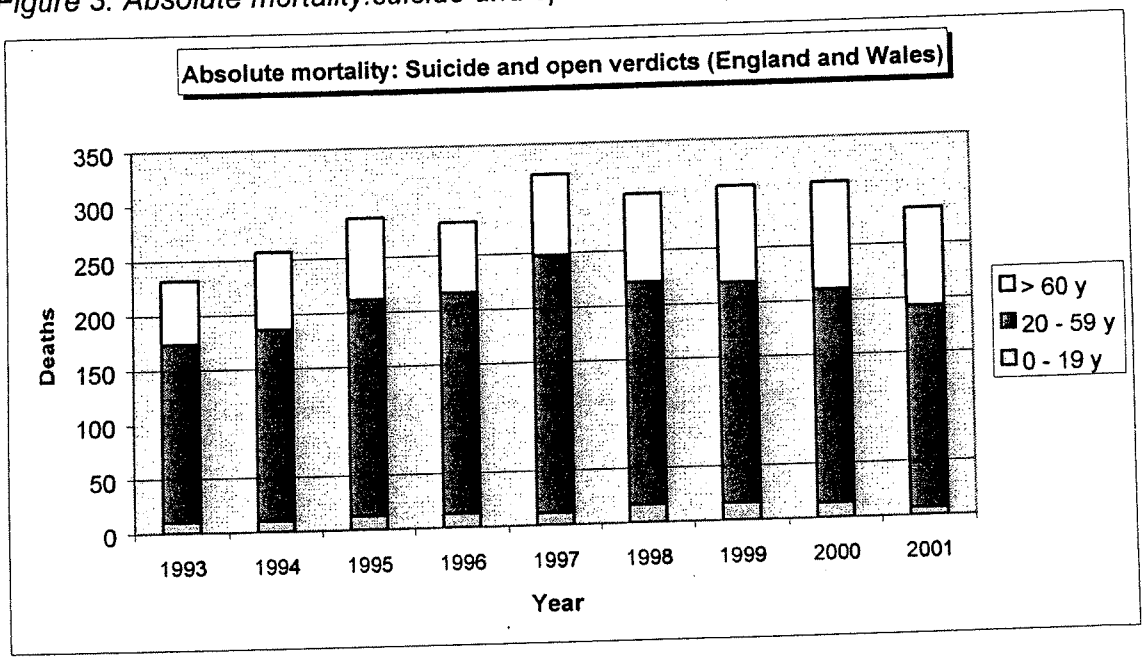
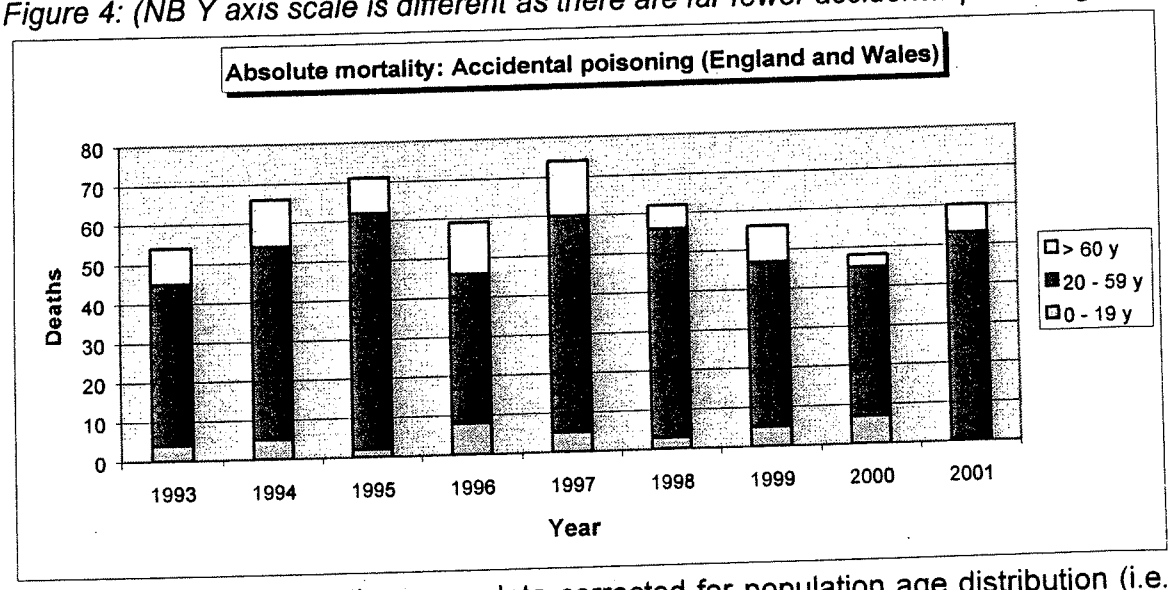


Figure 4: (NB Y axis scale is different as there are far fewer accidental poisonings)



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

Figure 5:

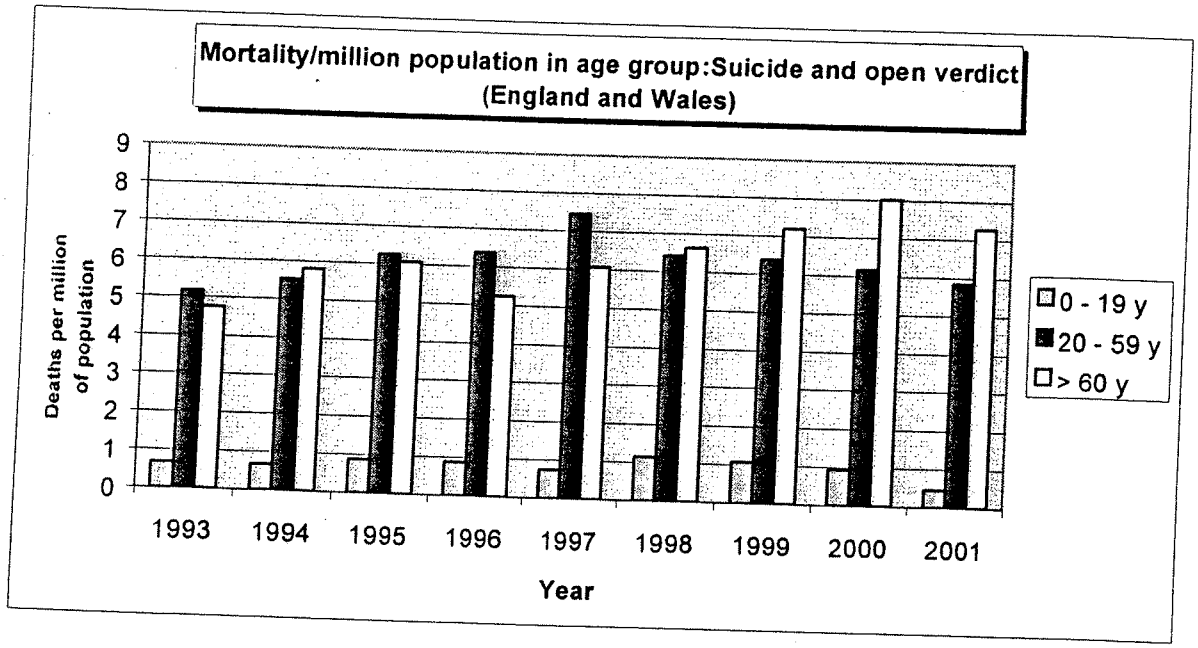
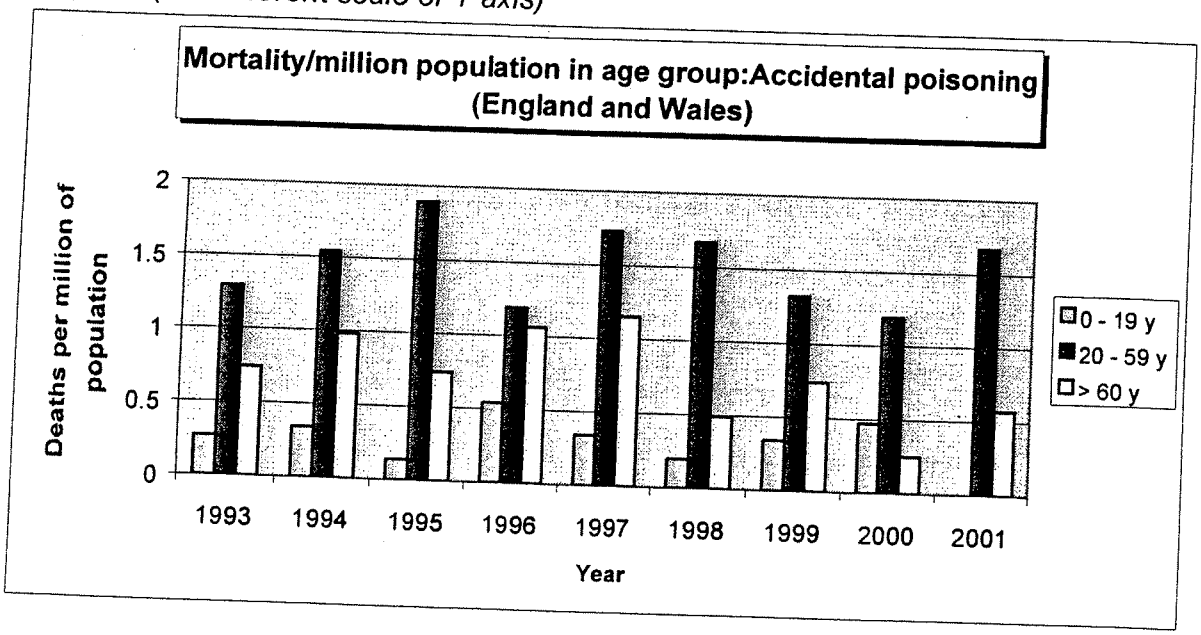


Figure 6: (NB different scale of Y axis)



6.2.2 ADROIT adverse drug reaction data

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

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

6.2.3 Morbidity data: Hospital data and data from Poisons Units

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

6.2.4 Enquiries to Poisons Centres

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

Telephone enquiries

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

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

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

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

TOXbase enquiries

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

6.3 Published Study of drug related suicides in England and Wales

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

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

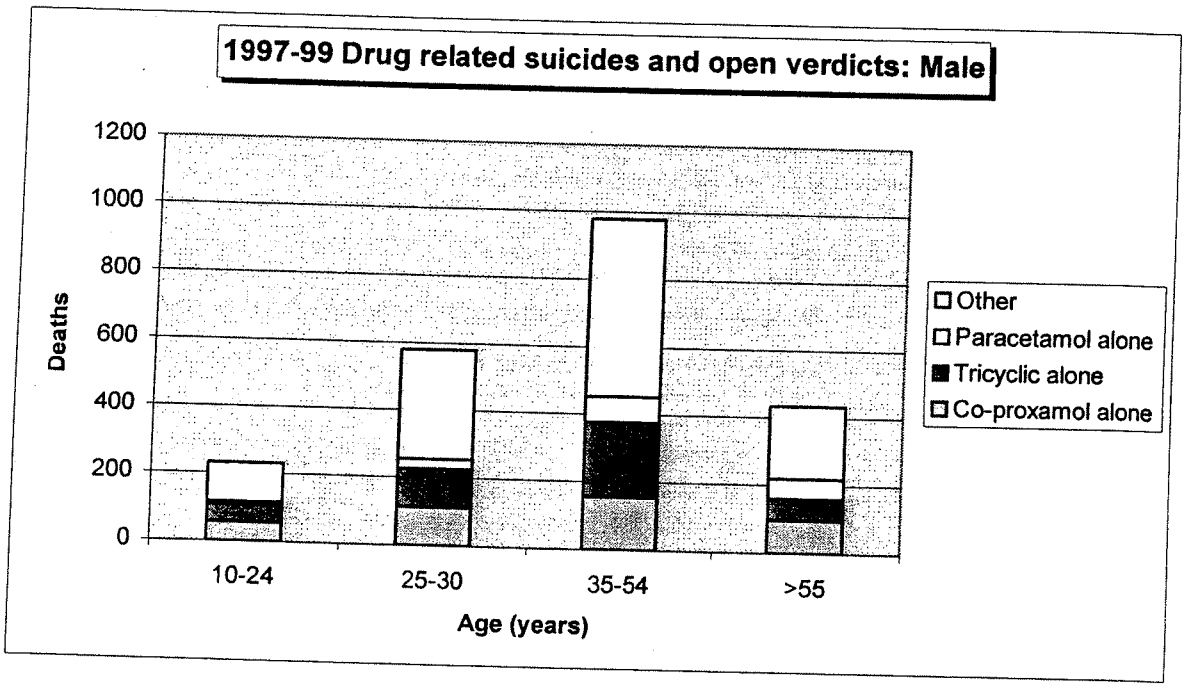
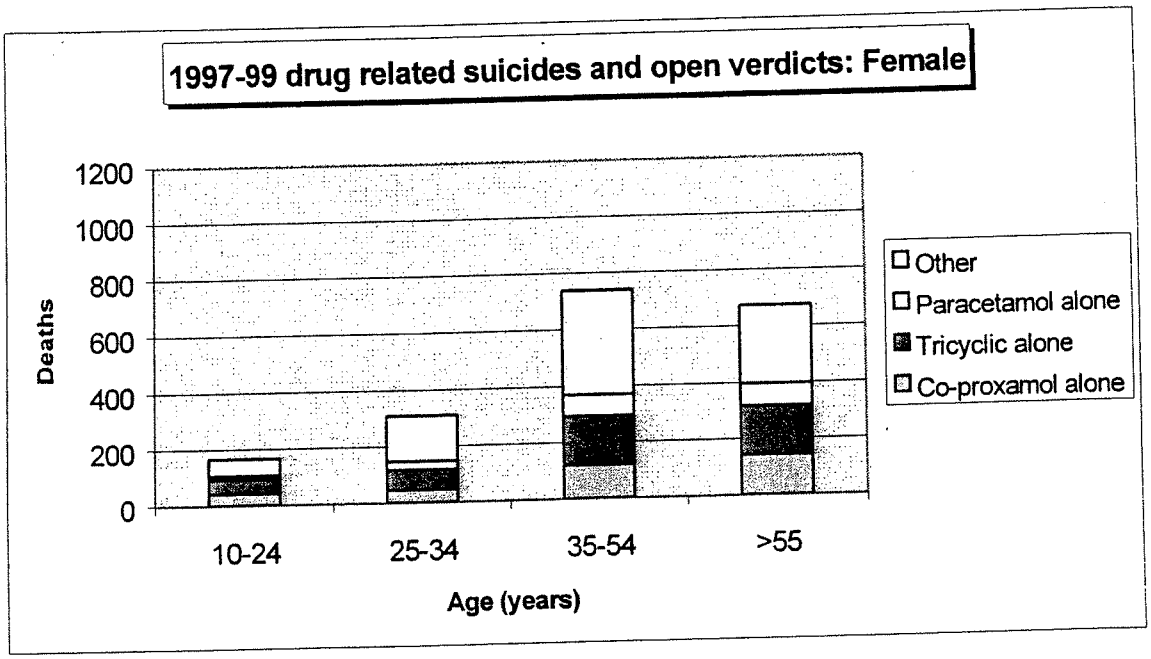


Figure 8: 1997-99 Drug related suicides and open verdicts (England and Wales): Female



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

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

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

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

6.4 Swedish data

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

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

7 SUCCESSFUL MEASURES TO REDUCE CO-PROXAMOL/DXP PRESCRIBING

7.1 UK initiatives

7.1.1 Doncaster

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

7.1.2 Northern Ireland

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

7.1.3 Nottingham

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

7.2 Sweden

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

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

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

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

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

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

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

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

7.3 Australia

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

7.4 Norway, Finland and Denmark

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

8 OPTIONS FOR ACTION

8.1 Revocation of licence

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

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

This is a rational restriction because:

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

Other prescribing restrictions for consideration are:

- ***Second line therapy only***

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

- ***Specialist use only***

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

8.3 Strengthen warnings in the product information

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

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

Key warnings in the PIL should be heavily emphasised:

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

8.4 Widen the range of available pack sizes

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

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

8.5 A co-ordinated programme of education and communication

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

- Focused dialogue with key influencers:
  - Hospital Formulary Committees
  - Royal Colleges (key medical specialties and nursing)
  - RPSGB

  Seminars or 'consensus meetings' following the Swedish model may have more impact than written communication with these influential individuals as the dialogue would be published by the participants in their professional journals.

- Awareness-raising campaigns in professional media:
  - MHRA website
  - Current Problems in Pharmacovigilance
  - CMO's Update (similar to the recent benzodiazepines warning at **Annex 27**)
  - Review article in a major medical journal
  - Further strengthening of the BNF warnings
  - Coverage by trade journals

9 CONCLUSIONS

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

- The toxicity of co-proxamol in overdose is well established; it is particularly hazardous because death occurs too rapidly for medical rescue. It now accounts for nearly one-fifth of all drug-related suicides in England and Wales.

- Efficacy superior to full dose paracetamol has not been adequately demonstrated for either acute or chronic pain

- Co-proxamol contains submaximal doses of paracetamol and as there is no evidence of synergy with dextropropoxyphene, it does not represent a rational fixed combination product.

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

10 ADVICE SOUGHT

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

10.1 Revocation of the marketing authorisations for co-proxamol

10.2 Restriction of indications to *chronic osteoarthritis, neuropathic pain and cancer pain*

10.3 Strengthening of product information, especially labels and leaflets

10.4 Encouraging the availability of a wider range of (smaller) pack sizes

together with:-

10.5 An education and communication strategy to change prescribing practice

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From the Rt Hon Dawn Primarolo MP
Minister of State

DH Department of Health

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79 Whitehall
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SW1A 2NS

Tel: 020 7210 3000

PO00000342663

[redacted]
House of Commons
Westminster
London SW1A 0AA

Dear [redacted]

02 OCT 2008

Thank you for your letter of 11 August enclosing further correspondence from your constituent [redacted] about the withdrawal of the painkiller co-proxamol.

May I take this opportunity to say again that I am sorry for the concern and inconvenience the decision has caused [redacted] This was not an easy decision and was the subject of careful consideration, consultation, expert advice and a focus of the best interest of public health.

I appreciate that [redacted] is unhappy with my earlier responses of 30 July and 17 June (our ref: PO00000330047 and PO00000311293). The problem with co-proxamol (a combination of the weak opiate painkiller dextropropoxyphene with a relatively low dose of paracetamol) is two-fold; the dextropropoxyphene component is extremely hazardous in overdose and there is little, if any, evidence that it offers an advantage over full strength paracetamol. Co-proxamol is involved in 300-400 self-poisoning deaths each year, of which around a fifth are accidental. These data come from the Office for National Statistics and relate to the number of deaths with a verdict of suicide. There is no information to indicate that these deaths involved drug addicts using the dextropropoxyphene component of co-proxamol, as [redacted] suggests in [redacted] email of 27 June.

[redacted] was concerned that he had not received a direct answer to the specific point he had made in that email. He had asked, if the Department is willing to allow a GP to prescribe on an unlicensed basis on their own responsibility, why is it not prepared for GPs to do so in all cases. Following a full review of the risks and benefits of co-proxamol, the Committee on Safety of Medicines (CSM) determined that the risks of co-proxamol clearly outweighed the benefits. As the Medicines and Healthcare products Regulatory Agency (MHRA) is legally bound to operate a licensing system based on the quality, safety and effectiveness of medicines, appropriate regulatory action had to be taken to cancel the licences for these products. Following consultation with pain management experts, the MHRA issued CSM Pain Management Guidance to help doctors find suitable alternatives for individual patients. We do, however, recognise that there are some patients who have not been

able to find a suitable alternative and therefore continued use of unlicensed co-proxamol for these patients is still possible, if their doctor considers it to be in their best interest. There is a clear provision in legislation which allows unlicensed medicines to be prescribed in this way. In the case of co-proxamol, removal of marketing authorisations, with continued use possible in exceptional circumstances, is the best balance that could be achieved.

The intention of the withdrawal of co-proxamol is to protect public health not to punish individual patients. Sometimes regulation has to balance the needs of the individual against the benefits at a population level. It is encouraging to see that the action taken is already having a positive impact on public health. In addition to the report from the national programme on Substance Abuse Deaths mentioned in previous correspondence, a recent study using data from Scotland has shown that the withdrawal of co-proxamol has been accompanied by a significant reduction in the number of deaths from co-proxamol overdose in Scotland and importantly a decrease in the number of overdose deaths overall. The authors of this study have estimated that around 300 lives per year in the UK will have been saved by the withdrawal of co-proxamol.

I hope this reply is helpful.

Yours ever,

Dawn

DAWN PRIMAROLO

MS(PH) - PO

[redacted]
House of Commons
London SW1A 0AA

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The Rt Hon Dawn Primarolo MP
Minister of State
Department of Health
Richmond House
79 Whitehall
London SW1A 2NS

11 August 2008

Dear Dawn

Thank you for your letter of 30 July (your ref: PO00000330047) about my constituent, [redacted] IP9 2BN.

I thought you should see a copy of the e-mail which [redacted] has sent me on 9 August.

[redacted]

WORKING FOR [redacted]
Constituency Office: [redacted]
Tel: [redacted] Fax: [redacted] E-mail: [redacted]

[redacted]

From: [redacted]
Sent: Saturday 09 August 2008 10:35
To: [redacted]
Subject: Re[redacted]

Dea[redacted]

Thank you for your letter of 5 August, enclosing the replies you have received from both the Minister of Health and [redacted]PCT.

I am extremely disappointed that **you** seem to have simply accepted the reply from the Health Minister in particular with nothing more than " I can appreciate that this may cause frustration", which is probably the biggest understatement for a very long while.

I posed a VERY SPECIFIC question in my E.mail of 27 July which has been TOTALLY IGNORED and apparently you too have either been unable to get a reply or have been unwilling to pursue a proper response for whatever reason, if you cannot what hope is there for us mere mortals??

It is SCANDALOUS that MP's and Ministers who are PUBLIC SERVANTS supposedly answerable to the Electorate are allowed to, and feel they are able, to treat the Taxpayer and individual with such utter disdain.

If the State wants something from me it has the right to expect me as a good citizen to provide full and honest replies otherwise it will "throw the book at me", but it seems that if I WANT SOMETHING I will have to face interminable waits for any kind of reply, and when and if one is forthcoming, I will only be given what the STATE wants me to know and hear, I am obliged to doff my cap say thank you sir and simply suffer in silence.

The very least I should be able to expect is common courtesy,openess, honesty and a straight reply to my very specific question,even the Minster of State is not and should not be immune to these basic requirements, but I suspect it shows just how far the traditional standards which have served Britain so well over many years have now simply dissapeared to be replaced by a total lack of caring for others, and an appaling self centred approach to almost everything.

I and thousands of other Arthritis sufferers are now virtually **condemmed** to a life of either constant pain(when there is a proven remedy) or taking an horrendous cocktail of drugs that give appalling side effects and are not even given a full explanation as to why this should be the case.

I suspect that for some pain suffers this situation could indeed **elevate the risk** of their "doing something silly" in an effort to obtain some relief, but I dont suppose that the Minister or indeed the PCT would turn a hair if this did happen, after all they have done their job havent they ??

I believe that this unwillingness to respond to my question in full,the seeming inablity for anyone to offer any real support in my situation and the decision to withdraw Co-Proxamol from thousands infringes my/ our Human Rights, and I now intend to take Legal Advice from a Solicitor,unless I have had a FULL reply to my question within 14 Days from the date of this E.Mail.(IE. 23 August 2008.)

The reply from [redacted] may make sense to her/yourself but is written in a way which is totally incomprehensible to simple people like myself and many others, there is a potential paralell with my own situation yet I am told that there "is nothing to worry about", try

asking numerous patients of [redacted] and other Practices) if they believe they are getting a "quality scheme" !!

All I am seeking is someone to REALLY listen, to understand,not to treat me like the Village Idiot, and to TRUST people like me to say/know what we feel is best for us, not to dictate a "solution" which in itself could I genuinely believe create more " problems" from people suffering pain .

If you have not already done so, may I suggest you speak with Dr Howard Stoate the Labour MP for Dartford who is far more qualified and involved in this situation than anyone else seems to want to be.

I await your reply please by 23 August, before taking the whole matter to Law to try and get some understanding and support.

Yours Sincerely

[redacted]

From: [redacted]
Sent: Friday 27 June 2008 11:01
To: [redacted]
Subject: [redacted]

Dear [redacted]
Thank you for your letter of 25 June, enclosing the reply you received from the Minister of State at the Department of Health, I am grateful to you for taking up the matter on my behalf.

Whatever I say in reply will no doubt be construed as either my having a vested interest in the

outcome, or born out of a growing frustration at the way these sort of decisions are made,but I would offer the following observations and be grateful if you could bring these to the attention of the Minister of State so that the genuine feelings of those affected are at least heard if not taken into account please.

My possibly less informed understanding of the background to the decision to withdraw was that there had been a number (300 or so) cases where death or possible suicide had been determined as coming from an abuse of Co-Proxamol, I fully accept that is 300 too many casualties.

However a large number of these were from "addicts"using a constituent part of Co-Proxamol to further their personal "habits", few if any were from regular users of the drug who needed it for their personal discomfort, and many of these were probably bought Online from Websites in America not dispensed by GP's.

Cannabis and other Class B/C drugs as well as many other "substances" kill many people directly and indirectly but these are not all the subject of such swingeing and indiscriminate withdrawls from those who need them , indeed they often seem to be encouraged.

It is hardly surprising that the Minister states " it is encouraging to see that a recent report from the national programme on Substance Abuse Deaths, shows that the number of deaths involving Co-Proxamol has declined since the Agency took action", fewer were in cthey had been withdrawn and were not available to those who needed them so fewer were in circulation surely an example of an irrelevant statistic being used to try and bolster a flawed decision??

It is encouraging to have confirmation that the Department still accepts and will allow a GP to prescribe on an Unliceneced basis (if one can be found) **but:**

1) That leaves the individual the task of looking for a needle in a haystack with no clues given as to where such a GP might be found.
2) The GP's (as shown by [redacted]) are taking the "easy" way out and hiding behind "we dont want to be sued" even when they admit the drug is probably in the best interest of their patient.
3) If the Department is willing to allow a GP to prescribe on an unlicenced basis at his/her own risk and thus accept the Doctors professional judgement, why are they not prepared for them to do so in all cases, surely GP's have not simply been handing out Co-Proxamol willy nilly, and if they have why have THEY not been punished rather than the patients ??

Whilst I applaud the "words" used by the Minister in her reply, that "this was not an easy decision and was the subject of careful consideration, consultation and expert advice,and a focus of the best interest of public health", I regret these are what I would expect to see and hear from a Politician, and are NOT in the best interests of patients who need pain relief and have achived this with Co-Proxamol for many years, surely GOOD GP's in conjunction with GENUINE patients could continue to do so "in the best interests of public health", or am I simply being too naive and using logic ??

For my own sake and those of others suffering from Arthritis I will continue to fight for a reappraisal of this appalling decision, but would ask please that these observations are passed to the Minister so that I at least know she has read the considered observations of a "real" patient **with a request that she responds in particular to my Question 3 Above, which currently defies all logic .**

Thank you again for your help to date, I look forward to hearing if you do receive a reply from the Minister because I cannot see how she/anyone can refute this specific question I have posed ?

Yours Sincerely

[redacted]

On 6/16/08, [redacted] ote:
Dear [redacted]
As it is now 4 weeks since [redacted] wrote to the Health Minister, dare I expect a formal response to my situation in the VERY near future or has my query been a victim of the current unfortunate epidemic of correspondence being allowed to travel on Public Transport on its own free of charge ??

To say that most normal people have lost complete and utter faith in the Political system and the ability of anyone from ANY Party to act efficiently would be a definite understatement, the situation is crying out for someone/ some Party to stand up and be counted, not in the way that David Davis has done, but simply to act quickly, openly, and above all professionally for the benefit of us all.

In the Sunday Express yesterday it reported that the Government had " admitted that it was not that Eastern European workers were stealing our jobs, rather that WE are too lazy to work in many instances" something many of us knew a long time ago, that it takes Government and all its back up resources 4 weeks plus to respond to a simple reasonable query which affects my personal wellbeing ,is hardly the role model to give to others and perpetuates the Im all right Jack attitude that pervades our Society.

I will watch my E.Mails and post with interest and if I have not received a reply by the end f this week at the latest, will consider what else I am forced to do to get a simple response.

[redacted]

On 6/6/08, [redacted] wrote:
Dear [redacted]
Thank you for your prompt response, obviously I have not yet received [redacted] letter otherwise I would not have been in touch again.

I am grateful for the information about the length of time it apparently takes a Minister to respond to a query, whilst I am sure the Minister is a busy person, it is just as well that this is not literally a case of imminent life and death, I am sure that IF the Minister wanted to know something FROM me, HE would expect a resposne in far less than four weeks, no wonder our Political system is now regarded by many as a complete joke and apathy reigns !!!

I look forward to receiveing the letter of 5 June, and importantly and interestingly the reply from the Minister in due course.

[redacted]

On 6/6/08, [redacted]
wrote:

Dear [redacted]

I can confirm that [redacted] wrote to you on 5 June.

It reads: "Thank you for your e-mail of 30th May. I wrote to the Minister at the Department of Health on 15th May and am still awaiting his response. It usually takes about 4 weeks for a Minister to reply to specific enquiries from Members of Parliament."

[redacted] will write to you again when he receives the Minister's letter.

Yours sincerely

[redacted]

020 72[redacted]

1. log & Ack.

2. [redacted]

[redacted]

Professor Sir Alasdair Breckenridge CBE
Chairman
Medicines & Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

[redacted]
Tel: [redacted]
Email: [redacted]

1st August 2008

Dear Sir Alasdair,

MHRA Withdrawal of Co-proxamol - Failure of MHRA "Named Patient" System

Just a courtesy letter to enquire whether there has been any change of policy to repair the collapse of the MHRA "Named Patient" system of Coproxamol prescription following MA licence withdrawal of 1st January 2008 ?

You will be aware that many insurers of GPs, and the UK doctor's *Medical Defence Union* have advised against co-operation with your defective policy ?

In general, I have given up corresponding with you, having exhausted all the MHRA internal review systems. After all, if the MHRA can ignore not one but two House of Commons Debates, and disregard criticism of your organisation by the House of Commons Health Select Committee, then what chance does an ordinary patient such as myself stand?

However, it is important, not for me, nor the thousands of patients your systemic collapse has left in unmanaged pain, but to you and your colleagues at the MHRA that I extend the courtesy of asking if you are looking to fix the collapse of your Coproxamol policy? This is so that I can review whether to withdraw the complaint currently being pressed against your registration as a doctor at the GMC [redacted]

In addition, whilst there has not been much publicity surrounding the Coproxamol mess, well not as much as the likes of the BBC television Panorama documentary on your Seroxat failures, there will be some stirrings in the form of a presentation at the initiative of BBC reporter, Julia George, whose own mother has been left in agony by your Coproxamol mess. The programme is scheduled to air on BBC Breakfast Television on 4th August 2008. Just thought you might like the heads-up.

Professor Sir Alasdair Breckenridge CBE
Chairman

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1 Nine Elms Lane
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SW8 5NQ

In the meantime, if you have had a change of heart and intent to fix the MHRA Coproxamol policy collapse, then please let me know, so that I can stop the alternate external prompts aimed at making the MHRA see some sense?

Next: I estimate that at least 1% of the original 1,700,000 patients annually prescribed Coproxamol are like me. Having found that all alternates are either too strong, too weak, or with intolerable side effects. This principle has been recognised by the House of Commons Adjournment Debates which you have chosen to ignore. That means, at your hand, orchestrating the direction of the MHRA, there has, in all probability, been an inhumane desertion of 17,000 patients left to live and die in untreated agony.

Dr Breckenridge, is this what you intended? Or is it the result of MHRA incompetence, refusal to listen, and a tragic result of the law of unintended consequences?

For the record, please can you confirm whether or not the MHRA have conducted, or commissioned any research or report to examine the results of the collapse of the MHRA "Named Patient" system of prescribing Coproxamol following MHRA MA licence withdrawal of 1st January 2008 ? Does the MHRA have any studies on how many of the original 1,700,000 patients prescribed Coproxamol have been left in a situation with no, or limited analgesia?

In fairness to yourself and the MHRA, please be advised that your response to this is likely to be published and placed in the public domain. So a direct answer would be appreciated. Thankyou.

Last but not least, I attach proof that your actions have contributed in my being exposed to a second round of spinal surgery. A copy of this, along with supporting documentation to progress my complaint against you, has also been submitted to the General Medical Council, Fitness to Practice Directorate.

I await your response as to what you intend to do about the 17,000 patients you and your colleagues at the MHRA may have condemned to live in untreated and unmanaged pain?

Yours faithfully,

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

30th July 2008

[redacted]

Dear [redacted]

[redacted] has requested the following appointment for you.

Examination : MRI Spine lumbar & sacral with contrast

Date of Appointment : Saturday 9th August 2008

Time : 11:00 am

Radiologist :

Please report to the Diagnostic Imaging 10 minutes before your appointment time.

If you have medical insurance, please inform the respective insurer of your appointment and obtain an authorisation number prior to attending. Please bring the name of your insurance company and your membership or registration number with you when you attend.

If you have any queries regarding this scan, please do not hesitate to contact the Diagnostic Imaging Department on [redacted]

Yours sincerely

[redacted]

[redacted]

[redacted]

From: [redacted]
Sent: 06 August 2008 11:23
To: [redacted]
Subject: Co-proxamol

Dear [redacted]

Thank you for your email about the withdrawal of the pain killer co-proxamol.

I am sorry that the withdrawal of co-proxamol is causing concern and inconvenience to some patients who, like you, have been taking co-proxamol without experiencing any problems and do not consider themselves to be at risk of deliberate or accidental overdose. This was not an easy decision to make and follows an extensive risk:benefit assessment, a wide consultation and advice from the Committee on Safety of Medicines (CSM) – the Government's former independent scientific advisory committee on medicine safety (now the Commission on Human Medicines) - and other experts.

The problem with co-proxamol (a combination of the weak opiate painkiller dextropropoxyphene with a relatively low dose of paracetamol) is two-fold; its dextropropoxyphene component is extremely hazardous in overdose and there is little, if any, evidence that it offers an advantage over full strength paracetamol. Co-proxamol is involved in 300-400 self-poisoning deaths each year, of which around a fifth are accidental. Many deaths involve people taking co-proxamol that had not been prescribed to them. Co-proxamol can be very toxic, and overdose can occur with only a few tablets more than the recommended daily dose. Death from co-proxamol overdose is extremely rapid compared with other pain relieving medicines so that victims often die before they reach hospital. Unlike paracetamol, there is no effective 'antidote' to co-proxamol poisoning. Whilst the dangers of co-proxamol are well-established, there is very little objective evidence that co-proxamol is any more effective in treating pain than normal paracetamol in the recommended dose. Furthermore, paracetamol is considered to have a comparatively good safety profile; onset of toxic effects is slow, allowing more time for rescue and a larger quantity of tablets is required to cause serious harm.

The CSM noted that previously strengthened warnings to doctors and patients on the hazards of co-proxamol had proved ineffective. After considering the wide range of available evidence and the options for action to reduce the risk of overdose (e.g. prescriber and patient education, smaller pack sizes and restricted indications) the CSM determined that the risks of co-proxamol clearly outweigh the benefits of allowing the medicine to remain on the market.

We recognise that there is a small group of patients who are finding it very difficult to change from co-proxamol and for these patients there is a provision in law for the supply of unlicensed co-proxamol, on the NHS. This is not an unusual arrangement and medicines may be supplied on this basis, but the responsibility for deciding whether or not to make use of that provision lies with the prescriber. The risks and benefits of the continued supply of an unlicensed medicine for individual patients must be weighed up by the prescriber in consultation with the patient.

understand from your email that your GP is not willing to prescribe unlicensed co-
roxamol in this way. Another doctor may be able to help and you may wish

second opinion. For example there may be a possibility of provision through a pain clinic at your local hospital, and your GP would need to authorise a referral.

The MHRA has sought legal advice on the possibility of a consent form to transfer the responsibility from the prescriber to the patient. The legal advice was that if unlicensed co-proxamol is prescribed, the doctor must take direct personal responsibility for this. A patient disclaimer/consent form cannot remove or satisfy that requirement as a doctor still has a responsibility to exercise his or her clinical judgment as well as a separate legal obligation to obtain informed consent to any treatment.

The decision to withdraw co-proxamol from the market has tested medicines regulation to the extreme. Weighed against the difficulty for individual users is the clear public health gain from the removal of a medicine which has been widely implicated in accidental and non accidental overdose. Sometimes regulation has to balance the needs of the individual against the benefits at a population level. In this case the removal of marketing authorisations with continued use possible in exceptional circumstances is the best balance that could be achieved.

Yours sincerely

[redacted]

From: [redacted]
Sent: 04 August 2008 22:14
To: [redacted]
Subject: Co-proxamol

Hi
Could you please help.

I have been on Co-roxamol for 8 years without any problems for very painful arthritis and now my GP won't prescribe it any more because it has been withdrawn.

Nothing else she has prescribed for me has helped because either they don't work or they have awful side effects.

I understand you say GPs are allowed to prescribe Co-proxamol on a named patient basis but why if that is okay won't she do so?

I even offered to sign anything to say it is totally my responsibility if anything were to go wrong but she or colleagues won't accept that.

I think after 8 years it is well known that this medication works for me and I can be trusted to be responsible for taking it.

On BBC breakfast this morning Dr. June Raine Medicines and Healthcare regulator said that GPs ARE allowed to prescribe Co-proxamol on a named patient basis.

[redacted] on the same program said she is still prescribing it.

Could you please clarify that this is the case and advise me what I or you can do about this?

Regards.

[redacted]

[redacted]

-----Original Message-----
From: [redacted]
Sent: 04 August 2008 10:09
To: [redacted]
Cc: [redacted]
Subject: MHRA Doctor Referral To GMC

Dear [redacted]

Unfortunately, I have to consider referring your Dr June Raine to the General Medical Council for alleged negligence, and/or bringing the medical profession into disrepute.

1. I need to establish whether Dr Raine is employed by the MHRA or retained as a consultant by the MHRA, or employed in any capacity by the MHRA? Please advise?

2. I need to establish whether Dr Raine was authorised to speak on national television for the MHRA and whether the MHRA stand by the wholly misleading information that Dr Raine gave on the BBC television programme? Please advise?

3. Please accept this communication as a formal complaint against Dr Raine? Please trigger the MHRA internal complaints process? My grounds are as follows:-

4. Dr Raine asserted on national television that "Coproxamol supplies are assured" and doctors are "not walking a legal tightrope". Dr Raine gave what can fairly be described as unfounded biased MHRA spin. The clear impression Dr Raine asserted was that patients requiring a clinical need for Coproxamol have been looked after and there is no problem with MHRA "named patient" policy on prescribing of Coproxamol. This is wholly and materially not the case. This GMC registered doctor has either publicly lied on national television, or been grossly negligent in preparing her brief for appearing on national television. I do not make such serious allegations lightly.

5. The MHRA know, or should know that the Medical Defence Union has issued blanket advice to their General Practitioner members NOT to prescribe Coproxamol on the MHRA "named patient" basis as IT IS A LEGAL TIGHTROPE. As a doctor, Dr Raine should know the advise of her Medical Defence Union?

6. The MHRA know, or should know that now, most Medical Practise Insurers have advised their client GPs throughout the UK, that their professional indemnity insurance does NOT cover the prescribing of Coproxamol on the "named patient" basis as devised by the MHRA.

7. It is clear that the MHRA "named patient" system of prescribing of Coproxamol has collapsed.

8. The MHRA require to repair this failed "named patient" system. Thus far the MHRA are in denial about the estimated 17,000 of patients that it's flawed safety net system has now left in untreated, or undertreated pain management. The BBC reporter Julia George had a better grasp of the issue than Dr Raine. Julia George asked why the

MHRA do not make Coproxamol either a "Hospital Only Drug" or a "Controlled Drug". In your reply, please can you answer this?

9. The MHRA safety net of "named patient" prescription of Coproxamol can now be proven to have been rejected by the majority of the medical pofession. What reason do you have to persuade me not to refer Dr Raine and any other misguided doctor at the MHRA to the General Medical Council Fitness to Practise Directorate?

10. On a purely personal, but clear example basis, as a result of having no Coproxamol pain management, I had to see a neurosurgeon last week. After examination he has ordered and MRI scan, and a second round of spinal surgery is proving more likely. Is this an acceptable result (one of many) of the flawed MHRA policy on Coproxamol?

If I fail to receive a reply within the next 10 days, I shall, without further correspondence with you, refer Dr Raine to the GMC. I have little time on this as I am in permanent chronic unremitting pain, with acute episodes, so giving the MHRA more time to sort out their mess is a luxury I cannot afford.

Yours sincerely,

[redacted]

4th August 2008

[redacted]

From: [redacted]
Sent: 16 December 2008 13:28
To: [redacted]
Subject: RE: Co-proxamol

Dear [redacted]

Thank you for your recent enquiry to the MHRA.

The decision to withdraw these licences has not been an easy decision to take and follows an extensive risk benefit assessment, a wide consultation and advice form experts and the Committee on Safety of Medicines (now known as the Commission on Human Medicines). The proposal to withdraw co-proxamol over an extended period of 3 years was to allow long term users the opportunity of finding suitable alternatives. To assist with this, the Agency has issued guidance on alternative strategies in a document titled 'CSM pain management guidance' which can be viewed at the link below', although it will obviously be for you and your doctor to decide between you on the optimal regime. We trust you will find an analgesic strategy that is satisfactory. Please find below links to the statements and guidance published on our website relating to the withdrawal of these licences:

http://www.mhra.gov.uk/NewsCentre/CON2025739

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2033395

We recognise that there is a small group of patients who are likely to find it very difficult to change from co-proxamol or where alternatives appear not to be effective or suitable. For these patients, following cancellation of the licences at the end of 2007 there is a provision for the supply of unlicensed co-proxamol, on the responsibility of the prescriber. To enable this to happen the brand leader has said that they will continue to manufacture unlicensed co-proxamol. Patients wishing to go down this route would need to discuss the possibility with their doctor, or the Prescribing Advisor of their local Primary Care Trust (PCT).

We can also confirm that there is no requirement for a member of the public to notify the MHRA of the importation of medicines for personal use and the legislation does not restrict such importation. Consequently, we do not issue any form of licence, certificate or authorisation to aid personal importation. The MHRA therefore has no objections, provided that the imported medicinal products is used only for your own personal use and that you do not sell or supply imported medicines to anybody else (including family members).

You should be aware that up to a 3 month supply of a medicine is considered to be an acceptable quantity for personal use, HM Revenue and Customs can prevent importation if large quantities are being imported and/or they have suspicions that the product is not being imported for personal use. You can read more about HM Revenue and Customs from their website at the link below:

http://www.hmrc.gov.uk/

In addition we recommend you refer to our website at the following link advice concerning the purchase of medicines over the internet:

http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Adviceandinformationforconsumers/Buyingmedicinesovertheinternet/index.htm

Please contact us again if you need further assistance with this, or any other queries.

Kind Regards,

[redacted]

-----Original Message-----
From: [redacted]
Sent: 12 December 2008 10:36
To: [redacted]
Subject: Co-proxamol

Hi there

I am writing with regard to the recent withdrawal of Co-proxamol from the list of available drugs in the UK.

I suffer from severe migraine and back pain on a fairly regular basis, and have until recently been using Co-proxamol to treat those conditions on a symptomatic basis. In fact I have been using Co-proxamol now for nineteen years and am thoroughly familiar with the drug, its effects on me, and what I can - and can't - do with the drug.

However, now that Co-proxamol has been withdrawn, I find that I have now no suitable painkiller with which to treat my ailments. No painkiller that my Doctor has tried has been suitable; for example, Tramadol makes me feel even more ill, as does any painkiller with codeine in it. Paracetamol barely scratches it, and specific migraine 'cures' such as Migraleve for some reason do not seem to work at all.

I realise that I am one small voice, but I would like to request that you reinstate Co-proxamol as an 'allowed' drug. Failing that, is there any way in which you can let me know of an alternative source of the product; I know there has been recent media attention regarding people buying 'foreign' drugs over the Internet, and I understand why this is dodgy. However, there are pharmacopoeias other than the British and European, and surely a product made under the US Pharmacopoeia would be safe? Not that I know if Co-proxamol is in the USP but my point is that there must be a foreign manufacturer whose products are safe!

I'm pretty desperate about this, though. The withdrawal of this product has had a profound effect on the management of my pain and therefore on my working life - and I work for the NHS too, so I suppose you could say that I am actually making the NHS less efficient, in some small way, because of my pain levels!

I do hope you can help me.

Cheers

[redacted]

Safeguarding public health

MHRA

[redacted]

[redacted]

16 December 2008

Dear [redacted]

Thank you for your letter of 11 December 2008 about the withdrawal of the pain killer co-proxamol. I am sorry to hear again of the difficulties the decision to withdraw co-proxamol is causing you.

Following a full review of the risks and benefits of co-proxamol, the Committee on Safety of Medicines (CSM) determined that there was no evidence of a benefit of co-proxamol over paracetamol but that co-proxamol was much more dangerous than paracetamol in overdose. Therefore the risks of co-proxamol clearly outweighed the benefits. As the Medicines and Healthcare products Regulatory Agency (MHRA) is legally bound to operate a licensing system based on the quality, safety and effectiveness of medicines, appropriate regulatory action had to be taken to cancel the licences for these products. On the other hand the benefit:risk balance for other analgesics such as Temgesic remains favourable which means that the benefits outweigh the risk of serious adverse reactions even in overdose. All drugs are monitored under the Yellow Card Scheme which is used to collect information from health professionals and patients on suspected adverse drug reactions. The MHRA continues to monitor the benefit:risk ratio of all medicines.

As stated in my previous letter, we do recognise that there are some patients who have not been able to find a suitable alternative to co-proxamol and therefore continued use of unlicensed co-proxamol for these patients is still possible if the doctor considers it to be in their best interest. This provision is set out in medicines legislation and is not an unusual arrangement although we do understand that use of this provision varies across the UK as it depends on individual prescribers taking responsibility for this.

I understand from your letter that your GP is not willing to prescribe unlicensed co-proxamol in this way. Another doctor may be able to help and you may wish to seek a second opinion. As medical defence organisations

[redacted]

are independent of Government the MHRA cannot comment on the cover provided by them for GPs who prescribe co-proxamol or any other unlicensed medicine. Individual GPs who have a concern over their indemnity cover should discuss this directly with the relevant organisation.

Finally you suggested that a pro forma letter could be used to support doctors in prescribing unlicensed co-proxamol. The MHRA has sought legal advice on the possibility of a consent form to transfer the responsibility from the prescriber to the patient. The legal advice was that if unlicensed co-proxamol is prescribed, the doctor must take direct personal responsibility for this. A patient disclaimer/consent form cannot remove or satisfy that requirement as a doctor still has a responsibility to exercise his or her clinical judgment as well as a separate legal obligation to obtain informed consent to any treatment.

Yours sincerely

[redacted]

11 December 2008

[redacted]

Dear Madam,
Thank you for your reply to my letter of Sept. 28th. May I first suggest you look at the evidence you provide more carefully – your penultimate paragraph, which suggests 300 lives have been saved since co-proxamol has become unavailable is logically equivalent to saying that if all cars are off the road there will be no car accidents!

Now back to my problem, which is still unsolved.. I have haemolytic anaemia, probably a side effect of the use of Avandia, discovered following your recent warning about its use, which prompted careful reading of the literature, to discover a 2% rate of anaemia as a side effect. I believe my consultant & GP are reporting this – and my blood count has risen towards normal following discontinuing the drug.

I am still on danazol, amongst whose side effects are muscular pain/spasms, which respond well to 2 co-proxamol in the morning, and 2 in the evening. Nothing else gives the same relief.
As I explained in my earlier letter, nothing else works as well – the nearest is ordinary aspirin, which works for about an hour, but gives me indigestion.
My GP has prescribed over my 25 years of osteo-arthritic pain a range of NSAID's – of which Volterol Retard was the most successful, until I became allergic to it. Now I see the BNF lists haemolytic anaemia as a side effect of many of them, and suggests all NSAID's cause blood changes, and the latest one I had prescribed, mefanamic acid (which did help a little), is known to cause haemolytic anaemia in some people. *So now NSAID's are off limits too*

Your paragraph suggesting my GP could prescribe co-proxamol is simply not true in practice, so I am left in disabling constant pain, while the MHRA committee absolve themselves of blame! My consultant actually prescribed co-proxamol for me at my last visit – only to have it rejected by the [redacted] as the Trust will not allow consultants to prescribe unlicensed drugs. My GP is in a similar position, as he has been instructed by his Insurers not to prescribe such drugs.

I ask again that you ask the committee to reconsider their approval, with appropriate safeguards. There are many dangerous drugs prescribed routinely - even the Temgesic I tried could have been abused in a manner to cause death! [redacted]

Alternatively, could they provide an appropriate pro forma for a letter absolving a doctor from any accusation of responsibility following the patient's misuse of the drug? Provided that he prescribes co-proxamol only in the circumstances you suggest, for those few patients who do find it difficult to change from it. This would overcome the medical insurance problem, and might focus the patient's attention.

I have been aware for the 20 years or so that I have occasionally used co-proxamol that a dozen or so with alcohol allowed [redacted] to commit suicide in comfort!

Yours faithfully.

[redacted]

Safeguarding public health

MHRA

[redacted]

[redacted]

3 December 2008

Dear [redacted]

Thank you for your letter of 27 November 2008 about the withdrawal of the pain killer co-proxamol.

I am sorry that the withdrawal of co-proxamol is causing concern and inconvenience to some patients who, like you, have been taking co-proxamol without experiencing any problems and do not consider themselves to be at risk of deliberate or accidental overdose. This was not an easy decision to make and follows an extensive risk:benefit assessment, a wide consultation and advice from the Committee on Safety of Medicines (CSM) – the Government's former independent scientific advisory committee on medicine safety (now the Commission on Human Medicines) - and other experts.

The problem with co-proxamol (a combination of the weak opiate painkiller dextropropoxyphene with a relatively low dose of paracetamol) is two-fold; its dextropropoxyphene component is extremely hazardous in overdose and there is little, if any, evidence that it offers an advantage over full strength paracetamol. Co-proxamol is involved in 300-400 self-poisoning deaths each year, of which around a fifth are accidental. Many deaths involve people taking co-proxamol that had not been prescribed to them. Co-proxamol can be very toxic, and overdose can occur with only a few tablets more than the recommended daily dose. Death from co-proxamol overdose is extremely rapid compared with other pain relieving medicines so that victims often die before they reach hospital. Unlike paracetamol, there is no effective 'antidote' to co-proxamol poisoning. Whilst the dangers of co-proxamol are well-established, there is very little objective evidence that co-proxamol is any more effective in treating pain than normal paracetamol in the recommended dose. Furthermore, paracetamol is considered to have a comparatively good safety profile; onset of toxic effects is slow, allowing more time for rescue and a larger quantity of tablets is required to cause serious harm.

During 2004, the CSM comprehensively reviewed all the available evidence regarding the risks and benefits of co-proxamol. A public call for evidence on

[redacted]

the risks and benefits of co-proxamol was also conducted for 12 weeks in 2004; the Medicines and Healthcare products Regulatory Agency (MHRA) wrote directly to a large number of organisations representing healthcare professionals, patient groups and other stakeholders as well as publishing the request for information on the MHRA website (www.mhra.gov.uk). Comments from patients and members of the public, as well as healthcare professionals were welcomed. The CSM reviewed all the responses to this call for evidence and also international evidence on the safety of co-proxamol.

The CSM noted that previously strengthened warnings to doctors and patients on the hazards of co-proxamol had proved ineffective. After considering the wide range of available evidence and the options for action to reduce the risk of overdose (e.g. prescriber and patient education, smaller pack sizes and restricted indications) the CSM determined that the risks of co-proxamol clearly outweigh the benefits of allowing the medicine to remain on the market.

The MHRA issued CSM pain management guidance to help doctors find the best options for individual patients. We recognise, however, that there is a small group of patients who are finding it very difficult to change from co-proxamol and for these patients there is a provision for the supply of unlicensed co-proxamol, on the responsibility of the prescriber. The brand leader is continuing to manufacture co-proxamol for this purpose. If you wish to go down this route you may wish to discuss this with your doctors.

It is encouraging to see that a recent report from the national programme on substance Abuse Deaths (np-SAD) based at [redacted]in London, shows that the number of deaths involving co-proxamol has declined since the CSM took action. Furthermore a recent study using data from Scotland has shown that the withdrawal of co-proxamol has been accompanied by a significant reduction in the number of deaths from co-proxamol overdose in Scotland and importantly a decrease in the number of overdose deaths overall. The authors of this study have estimated that around 300 lives per annum in the UK will have been saved by the withdrawal of co-proxamol.

The decision to withdraw co-proxamol from the market has tested medicines regulation to the extreme. Weighed against the difficulty for individual users is the clear public health gain from the removal of a medicine which has been widely implicated in accidental and non accidental overdose. Sometimes regulation has to balance the needs of the individual against the benefits at a population level. In this case the removal of marketing authorisations with continued use possible in exceptional circumstances is the best balance that could be achieved.

Yours sincerely

[redacted]

[redacted]

27-11-08.

Dear Sir/Madam.

My name is [redacted], I'm 64 years old, and I've got Rheumatoid Arthritis, I started having symptoms from an early age I think I was about 12/13 but I wasn't actually diagnosed until the middle eighties I must admit that to look at me, most people wouldn't believe I had R.A. as I have no joint distortion, as my bones don't pitt as most R.A. sufferers do.

But my R.A factor keeps going continuously and I have short sharp very painfull flare-ups

I also have an intolerance to any thing that is aspirin based, this wasn't discovered until my initial diagnosis, as my stomach problems were misdiagnosed as having some sort of ulcer.

So we had to find a new pain relief which after much a to-do turned out to be Co-proximal. And oh! how it reformed my life

I'm not very good with drugs, not bodily or mentally, but my body accepted co-proximal with such a huge sigh of relief and I started to experience a pain free life, which was Wonderfull. I also knew co-proximal was a dangerous drug if abused from my GP

and I was regularly monitored, and when new anti-inflamatory drugs came on to the market, we would try them, all to no avail
But unfortunately deaths kept occuring by either accident or deliberate overdoses that restrictions were applied, and I became a named user of co-proxiMal via our local P.C.T. That was until March this year, I found out to my horror that co-proximal had been with drawn entirely, and my life turned from being reasonably tolerable to one of pain, misery, and bewilderment and the only pain killer I had left, which frankly doesn't touch the sides, was paracetamol My G.P. and myself retried old pain killers and any new one, but all to no avail.
So a referal to the pain clinic was the next step, which has proved difficult by circumstances, but I finally got an appointment for 13th February 2009 which I knew was tootoo long, and I heard yesterday that the appointment has been bought forward to 19th December 2008
What I felt was needed was for M.H.R.A. to know how your decision to with draw co-proximal, how ever well meaning your decision was, the repercussions for me have been awfull.
I would never wish for any body to suffer with R.A. for its an awfull pity less miserable bloody illness.
I would like you to promise that infuture when you decide to with draw

drugs, that you replace it with something as comparable, but not as dangerous, and you talk to the people who will actually be affected by its withdrawal

Thank you for your time, and that something like this never happens again I've enclosed a copy of my medication for your perusal.

Yours faithfully

[redacted]

P.S Sorry about spelling + wording

ent ID : [redacted]

otrexate Tablets 2.5 mg [ ]
g (eight tablets) to be taken weekly
t : 32 tablet
Issued : 19.11.2008

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nisolone E/C Tablets 2.5 mg [ ]
TO BE TAKEN DAILY
t : 100 tablet
Issued : 18.11.2008

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dronic Acid Tablets 70 mg AS FROM 20-11-08 [ ]
TO BE TAKEN WEEKLY UNABLE TO TOLERATE. WILL BE REPLACED
t : 2x4 tablet
Issued : 6.11.2008

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ichew D3 Forte Chewable Tablets [ ]
ILY EXCEPT DAY OF ALENDRONATE
t : 200 tablet(s)
Issued : 6.11.2008

PATIENTS – please read the notes overleaf

Patient ID : [redacted]

Date Printed :19/11/2008

Temazepam Tablets 10 mg [ ]
ONE TO BE TAKEN AT NIGHT
Quant : 56 tablet
Last Issued : 6.11.2008

Paracetamol Caplets 500 mg [ ]
TWO TO BE TAKEN FOUR TIMES DAILY
Quant : 200 tablet
Last Issued : 6.11.2008

Sulfasalazine E/C Tablets 500 mg [ ]
TWO TO BE TAKEN TWICE A DAY
Quant : 112 tablet(s)
Last Issued : 18.11.2008

Omeprazole Capsules (Gastro-Resistant) [ ]
20 mg
1 DAILY
Quant : 2x28 capsule
Last Issued : 18.11.2008

Prednisolone Tablets 1 mg [ ]
REDUCING DOSE.
Quant : 4x28 tablet
Last Issued : 20.10.2008

Folic Acid Tablets 5 mg [ ]
1 WEEKLY ON FFIDAY
Quant : 14 tablet
Last Issued : 15.9.2008

Review Date : 16/01/2009

PATIENTS – please read the notes overleaf

[redacted]

From: [redacted]
Sent: 22 October 2008 10:21
To: [redacted]
Subject: RE: Withdrawal of CO-PROXAMOL

Dear [redacted]

Thank you for your email about co-proxamol.

With regards to your point about the impact of the withdrawal of co-proxamol, it is encouraging to see that a recent report from the national programme on substance Abuse Deaths (np-SAD) based at [redacted] in London, shows that the number of deaths involving co-proxamol has declined since the CSM took action. Furthermore a recent study using data from Scotland has shown that the withdrawal of co-proxamol has been accompanied by a significant reduction in the number of deaths from co-proxamol overdose in Scotland and importantly a decrease in the number of overdose deaths overall. The authors of this study have estimated that around 300 lives per annum in the UK will have been saved by the withdrawal of co-proxamol.

Yours sincerely

[redacted]

From: [redacted]
Sent: 18 October 2008 10:13
To: [redacted]
Subject: Re: Withdrawal of CO-PROXAMOL

Dear [redacted]

Thank you for clarifying the position with respect to the withdrawal of licences for co-proxamol. I have read the advice on analgesic options in treatment in mild to moderate pain in adults that you referred me to. I cannot take Ibuprofen and my GP wouldn't prescribe it even if I could because he has grave concerns about the side effects upon the lining of the bowel.I am one of a group of people for whom codeine is ineffective for pain relief. I have been taking anti-convulsants for some years having discovered they might be helpful through Action for ME. I am taking the recommended dose for trigeminal neuralgia, i.e.100mg three times a day.

Non drug interventions like acupuncture have been tried and do not work on the symptoms of ME/CFS or pain and stiffness in multiple joints. It did improve my quality of sleep for some time, however. TENS machines do not work for ME/CFS. A chiropractor might be able to help but I cannot afford alternative treatments.I have tried the newer and older type anti-depressants and they have no effect on my symptoms, largely because I am not depressed. I have to manage my symptoms with bedrest during the day now which I did not have to do before co-proxamol was withdrawn. This feels like a huge waste of my time and talents, [redacted]

I will talk to my GP about trying more potent opioids but the damage to my joints through lack of exercise is now irreversible. The MHRA have put me where I am and I do not think it fair that more research was not done on the possible impact on patients in the long term before the drug was withdrawn permanently. Caffeine could have been added to lessen the anti-tussive effect of the drug and improve its impact on pain. Nobody seems to have considered this.

I doubt if the absence of co-proxamol has had any significant impact on the number of suicides in the interim since if a person is in that state of mind, sadly, there is little that can be done to prevent them taking their lives by other means.

Yours sincerely,

[redacted]

----- Original Message -----

From: [redacted]
To: [redacted]
Sent: Friday, October 17, 2008 11:12 AM
Subject: RE: Withdrawal of CO-PROXAMOL

Dear [redacted]

Thank you for your recent enquiry to the MHRA. We apologise if our previous reply was ambiguous and can confirm the decision was taken in January 2005 and the licenses were cancelled 3 years from this date, at the end of December 2007.

Please contact us again if you need further assistance with this, or any other queries.

Kind Regards,

[redacted]

From: [redacted]
Sent: 15 October 2008 08:18
To: [redacted]
Subject: Re: Withdrawal of CO-PROXAMOL

Dear Sirs,

It is unclear when the 3 year period of withdrawal of co-proxamol will end. Can you please confirm end date??

[redacted]

----- Original Message -----
From: [redacted]
To: [redacted]
Sent: Tuesday, October 14, 2008 2:56 PM
Subject: RE: Withdrawal of CO-PROXAMOL

Dear [redacted]

Thank you for your recent email to the [redacted] concerning the withdrawal of co-proxamol.

The decision to withdraw these licences has not been an easy decision to take and follows an extensive risk benefit assessment, a wide consultation and advice form experts and the Committee on Safety of Medicines (now known as the Commission on Human Medicines). The proposal to withdraw co-proxamol over an extended period of 3 years was to allow long term users the opportunity of finding suitable alternatives. To assist with this, the Agency has issued guidance on alternative strategies in a document titled 'CSM pain management guidance' which can be viewed at the link below', although it will obviously be for you and your doctor to decide between you on the optimal regime. We trust you will find an analgesic strategy that is satisfactory. Please find below links to the statements and guidance published on our website relating to the withdrawal of these licences:

http://www.mhra.gov.uk/NewsCentre/CON2025739

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2

At the end of January 2005 the MHRA communicated the decision that the painkiller co-proxamol was to be withdrawn from the market. This followed a 12-week exercise to gather further information on the risks and benefits of co-proxamol. A decision was made to withdraw co-proxamol over a phased period of time – until the end of 2007 – to give patients a chance to move to suitable alternatives.

The marketing authorisations (MAs) for co-proxamol were cancelled at the end of 2007. Following withdrawal of the MAs it remains legal to continue to supply co-proxamol released into the normal distribution chain prior to 31 December 2007 up until the product expiry date on the label has passed.

We recognise that there is a small group of patients who are likely to find it very difficult to change from co-proxamol or where alternatives appear not to be effective or suitable. For these patients, following cancellation of the licences at the end of 2007 there is a provision for the supply of unlicensed co-proxamol, on the responsibility of the prescriber. To enable this to happen the brand leader has said that they will continue to manufacture unlicensed co-proxamol. Patients wishing to go down this route would need to discuss the possibility with their doctor, or the Prescribing Advisor of their local Primary Care Trust (PCT).

Please contact us again if you need further assistance with this, or any other queries.

Kind Regards,

[redacted]

From: [redacted]
Sent: 14 October 2008 09:27
To: [redacted]
Subject: Withdrawal of CO-PROXAMOL

Dear Sirs,

I suffer from ME/CFS and Osteo-Arthritis and found my symptoms well managed on CO-PROXAMOL. Since its withdrawal I have not been able to exercise as much. Because of this I have lost a lot of movement in my joints, have great difficulty walking, have become seriously overweight, have high blood lipids and am hypertensive. The alternative painkillers like CO-DYDRAMOL are less effective and have side effects that mean I can only take them once a day. PARACETEMOL alone has no discernable effect on my symptoms. I am on DICLOFENAC which is contraindicated for someone my age - I am 61. The present regime does not meet my health needs. This is not a situation I would have found myself in if a valuable and effective drug like CO-PROXAMOL had not been withdrawn. I have contact with quite a few other disabled people who used to rely on the drug who find themselves in a position similar to mine.

I would welcome your comments on this.

[redacted]

[redacted]

From: [redacted]
Sent: 23 September 2008 15:25
To: [redacted]
Subject: RE: co-proxamol

)ear Enquirer,

Thank you for your recent email to the [redacted] concerning the withdrawal of co-)roxamol.

The decision to withdraw these licences has not been an easy decision to take and follows an extensive risk benefit assessment, a wide consultation and advice form experts and the Committee on Safety of Medicines (now known as the Commission on Human Medicines). The proposal to withdraw co-proxamol over an extended period of 3 years was to allow long term users the opportunity of finding suitable alternatives and to assist with this, the Agency issued guidance on alternative strategies.

At the end of January 2005 the MHRA communicated the decision that the painkiller co-proxamol was to be withdrawn from the market. This followed a 12-week exercise to gather further information on the risks and benefits of co-proxamol. A decision was made to withdraw co-proxamol over a phased period of time – until the end of 2007 – to give patients a chance to move to suitable alternatives.

We recognise that there is a small group of patients who are likely to find it very difficult to change from co-proxamol or where alternatives appear not to be effective or suitable. For these patients, following cancellation of the licences at the end of 2007 here is a provision for the supply of unlicensed co-proxamol, on the responsibility of the prescriber. To enable this to happen he brand leader has said that they will continue to manufacture unlicensed co-proxamol. Patients wishing to go down this route vould need to discuss the possibility with their doctor, or the Prescribing Advisor of their local Primary Care Trust (PCT).

Please note that GP's are able to prescribe, and if your GP is willing it sounds from your account that either the [redacted] (or possibly your [redacted]) are presenting the obstacle and we advise you discuss this with your GP or Prescribing Advisor to ascertain the barriers to obtaining this.

Kind Regards,

[redacted]

From: [redacted]
Sent: 23 September 2008 10:19
To: [redacted]
Subject: co-proxamol

am devastated by your withdrawal of this drug. I have suffered from Arachnoiditis for 30 years and it has given me side-effect ree relief. Paracetemol is no substitute whatever and should I wish to kill myself I could do it with any number of 'over the counter' drugs. My pharmacist could dispense it, my GP is willing to prescribe it but is not permitted to do so. Please give this omewhat arbitrary and ill-researched decision more thought. I am well over 86 years and it seems a great pity to have to pend my remaining years in unnecessary pain. Sincerely, [redacted]

[redacted]

From: [redacted]
Sent: 20 October 2008 11:56
To: [redacted]
Subject: RE: Co-proxamol

Dear [redacted]

Thank you for your recent enquiry to the MHRA.

As you are aware, the marketing authorisations (MAs) for co-proxamol were cancelled at the end of 2007. However, following withdrawal of the MAs it remains legal to continue to supply co-proxamol released into normal distribution chain prior to 31st of December 2007 up until the product expiry date on the label has passed. This information is confirmed on our website at the following link:

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON2033

If you believe [redacted] are supplying stocks outside of the scenario outlined here, we would be grateful if you could send us full details of your concerns so we can investigate this further.

Please contact us again if you need further assistance with this, or any other queries.

Kind Regards,

[redacted]

From: [redacted]
Sent: 16 October 2008 15:31
To: [redacted]
Subject: Co-proxamol

To whom it may concern,

It has come to our attention whilst working in GP practices that [redacted] are currently supplying co-proxamol tablets through normal routes and not on a named patient basis. This is something that my team felt that you should be aware of.

Kind Regards,

[redacted]

Before printing, think about the environment

Safeguarding public health

MHRA

[redacted]

Tel: [redacted]

Fax: [redacted]

Email: [redacted]

21 October 2008

Dear [redacted]

Thank you for your letter of 28 September 2008 about the withdrawal of the pain killer co-proxamol.

I am sorry that the withdrawal of co-proxamol is causing concern and inconvenience to some patients who, like you, have been taking co-proxamol without experiencing any problems and do not consider themselves to be at risk of deliberate or accidental overdose. This was not an easy decision to make and follows an extensive risk:benefit assessment, a wide consultation and advice from the Committee on Safety of Medicines (CSM) – the Government's former independent scientific advisory committee on medicine safety (now the Commission on Human Medicines) - and other experts.

The problem with co-proxamol (a combination of the weak opiate painkiller dextropropoxyphene with a relatively low dose of paracetamol) is two-fold; its dextropropoxyphene component is extremely hazardous in overdose and there is little, if any, evidence that it offers an advantage over full strength paracetamol. Co-proxamol is involved in 300-400 self-poisoning deaths each year, of which around a fifth are accidental. Many deaths involve people taking co-proxamol that had not been prescribed to them. Co-proxamol can be very toxic, and overdose can occur with only a few tablets more than the recommended daily dose. Death from co-proxamol overdose is extremely rapid compared with other pain relieving medicines so that victims often die before they reach hospital. Unlike paracetamol, there is no effective 'antidote' to co-proxamol poisoning. Whilst the dangers of co-proxamol are well-established, there is very little objective evidence that co-proxamol is any more effective in treating pain than normal paracetamol in the recommended dose. Furthermore, paracetamol is considered to have a comparatively good safety profile; onset of toxic effects is slow, allowing more time for rescue and a larger quantity of tablets is required to cause serious harm.

[redacted]

The CSM noted that previously strengthened warnings to doctors and patients on the hazards of co-proxamol had proved ineffective. After considering the wide range of available evidence and the options for action to reduce the risk of overdose (e.g. prescriber and patient education, smaller pack sizes and restricted indications) the CSM determined that the risks of co-proxamol clearly outweigh the benefits of allowing the medicine to remain on the market. You suggested that co-proxamol prescribing should be restricted to the elderly. Up until 1997 the mortality rate (death per million) was greatest in 20 to 59 year olds. Since 1998, however, the risk has been greatest in people aged greater than 60 years and mortality in the under 20s is extremely small in comparison with adults. Furthermore, many deaths involve people taking co-proxamol that had not been prescribed to them. With this in mind it would not be appropriate to restrict prescribing of co-proxamol according to age.

The MHRA issued CSM pain management guidance to help doctors find the best options for individual patients. We recognise, however, that there is a small group of patients who are finding it very difficult to change from co-proxamol and for these patients there is a provision for the supply of unlicensed co-proxamol, on the responsibility of the prescriber. The brand leader is continuing to manufacture co-proxamol for this purpose. If you wish to go down this route may I suggest you discuss this possibility with your doctor.

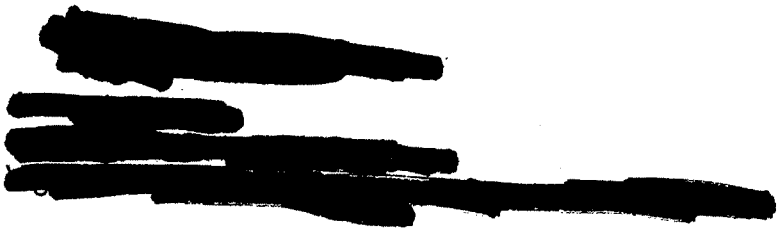
The Government takes the prevention of suicide very seriously. Suicide is a major public health issue. Around 4,500 people take their own life in England every year. A national suicide prevention strategy was launched in 2002, which sets the target of reducing the death rate by suicide by at least one-fifth by 2010. An important aspect of the strategy is to reduce the number of suicides as a result of self-poisoning.

The National Institute for Mental Health in England (NIHME) advise that reducing access to lethal methods of self-harm is known to be an effective way of preventing suicide. One reason is that suicidal behaviour is sometimes impulsive, so that if a lethal method is not immediately available a suicidal act can be delayed or prevented altogether. Although "method substitution" does occur, a number of people will not go on to use another method and lives can therefore be saved. In light of this evidence, the withdrawal of co-proxamol represents an important move towards reducing the number of suicide deaths each year.

It is encouraging to see that a recent report from the national programme on substance Abuse Deaths (np-SAD) based at St George's Hospital in London, shows that the number of deaths involving co-proxamol has declined since the CSM took action. Furthermore a recent study using data from Scotland has shown that the withdrawal of co-proxamol has been accompanied by a significant reduction in the number of deaths from co-proxamol overdose in Scotland and importantly a decrease in the number of overdose deaths overall. The authors of this study have estimated that around 300 lives per annum in the UK will have been saved by the withdrawal of co-proxamol.

The decision to withdraw co-proxamol from the market has tested medicines regulation to the extreme. Weighed against the difficulty for individual users is the clear public health gain from the removal of a medicine which has been widely implicated in accidental and non accidental overdose. Sometimes regulation has to balance the needs of the individual against the benefits at a population level. In this case the removal of marketing authorisations with continued use possible in exceptional circumstances is the best balance that could be achieved.

Yours sincerely



From: [redacted]
Sent: 15 October 2008 14:52
To: [redacted]
Subject: CO- PROXAMOL

I attach (as a word 93 document) a letter I sent to NICE, who tell me it should be sent to your committee. I would be grateful if you will pass it to the chair of the appropriate committee for reply.

[redacted]

[redacted]

28 September 2008

[redacted]

Dear Sir,

I wish to complain about the decision of your committee to ban the use of co-proxamol. As an arthritis suffer I have used this drug for many years with no ill effect whereas the n-saids and other groups of drugs have either gradually become ineffective or have been discovered to have nasty side effects in the longer term. Your decision appears to have been taken without any effective replacement being in place and has been implemented, by so frightening G.P.s with the loss of legal protection, that they, (very understandably), will not prescribe it, although I am told by my consultant and other medics, that strictly, it is still available. Meanwhile the drug companies have reacted predictably by increasing its price tenfold.

In my case I was offered paracetamol as an alternative, a drug I discovered some 40 years ago disagreed with me so violently that I spent a week in bed with violent stomach cramps, sickness and diarrhoea after the only occasion I ever took any. Since the withdrawal of co-proxamol, my doctor has tried many possible drugs as an alternative with no result. They either don't afford any relief at all or have unwanted side effects, sickness, feelings of nausea, but mostly diarrhoea. The latest alternative being temgesic and associated patches, a prescription only narcotic, very much more expensive for the N.H.S. and one I would much rather not have dealings with. This is also causing stomach problems.

Two years ago I contracted haemolytic anaemia and the rather powerful drugs being used to treat this can also cause similar effects. From my point of view it would be much wiser to have to deal with one variable, i.e. the treatment of the haemolytic anaemia, and keep the arthritis treatment constant on co-proxamol amid the turmoil of the treatments for haemolytic anaemia, which themselves have caused dangerous side effects (one deprived me of any white blood cells and I was returned to hospital in a hurry).

While on co-proxamol I rarely needed to take more than (2X2) tablets per day (half the permitted daily amount) whereas with every alternative so far I've needed the maximum permitted.

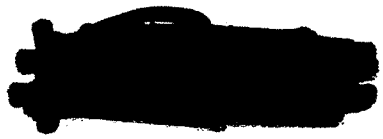
There are many elderly people suffering as I am with no viable alternative to co-proxamol to ease their aches and pains (Your decision does seem to be particularly hard on the elderly, an ageism decision?) and extrapolating from those I know, there must be tens of thousands, country wide, in the same boat.

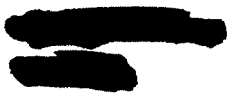
So far as I have been able to discover your reason for your draconian decision was a belief that it makes suicide too easy to obtain, and not because of any known harm it may cause in normal use. Surely it would have been better to control the amount of co-proxamol in circulation by other means such as making it subject to the same rules as temgesic, or restricting the amount to be issued at any one time, or even, since the fear of suicide seems to be among the young, restricting the age of the patient to whom it may be prescribed. Those of us who have benefited by the use of this drug for many years and therefore are mainly elderly) are hardly likely to rush out and commit suicide. We would much rather enjoy the time left to us with as little pain as possible

One is tempted to add that surely your remit is to get the best possible and safest drugs for the citizens if this country at the best possible prices, not to ensure that those with suicidal tendencies must die in the most painful ways possible.

The reason and conditions which induce some to such a state that they contemplate suicide are many and complex but to attempt to safeguard them by forcing many thousands of others, mainly elderly, to live in pain, is both cruel and naive. I do beg you to seriously reconsider your decisions and allow the use of this drug again albeit with restrictions of some sort.

Yours faithfully,



CC 

[redacted]

From: [redacted]
Sent: 16 October 2008 13:19
To: [redacted]
Subject: FW: Co-proxamol

Dear [redacted]

Thank you for your email. I am responding as the MHRA is responsible for the licensing of medicines in the UK.

We are not aware of any evidence that people of low weight are at any more risk of accidental overdose with coproxamol than those of normal to high weight. Co-Proxamol was licensed for many years at a standard dose for all adults of 1-2 tablets 3-4 times daily to a maximum of 8 tablets in 24 hours.

The MDU is already aware of the provision in law for the supply of unlicensed medicines and their website includes advice for doctors on the key issues to be considered before an unlicensed medicine is prescribed.

I am sorry but there is no further advice I can give you on this matter.
Yours sincerely

[redacted]

From: [redacted]
Sent: 10 October 2008 10:22
To: [redacted]
Cc: [redacted]
Subject: RE: Co-proxamol

I note your response to my communication but it was addressed to the DoH, not just the MHRA, and I shall request a direct response from them.

I find your assertion that the critical dose is not dependant on the size of the patient quite incredible. I challenge you to find a reference that would substantiate this assertion. All LD50 figures, for example, are quoted per Kg of body mass.
The toxicity when taken with alcohol is ill-defined. It would be a valuable research topic for a forensic pathologist to collect and collate data on this aspect.
I used the term "cost\benefit" analysis loosely when I meant, and should have said, "risk\benefit" analysis; apologies

My suggestion regarding contacting the MDU was based on the "provision in law" statement from [redacted] and others. Please tell the MDU that, since this provision in law exists they should pass it on to their membership as a specific exception to the normal rules governing prescription of unlicensed drugs in order to circumvent the current situation which is ludicrous:

* "Post Code" lottery – minority of GPs "breaking ranks" (and on a "per GP" rather than a "per patient" basis)
* Patients buying un-prescribed, uncontrolled substitutes from overseas

* Hospital pain clinics can prescribe co-proxamol once only.

I understand my local MP, [redacted] is to write to DoH reinforcing this request. Whether the MDU's instruction regarding co-proxamol applies to any other unlicensed drug as well is irrelevant, the effect is to negate the "provision in law" for co-proxamol for specific patients.

To continue like this is bureaucratic nonsense.
The restriction of prescription to a "hard core" of <60000 patients had already greatly reduced the overdose casualties
Angry patients will not go away until some action is taken
I am appealing to the DoH to "call their Agency to order" over this.

If you can give me no further advice on this matter I suggest you find someone more senior who is capable of appreciating the current paradox.

[redacted]

[redacted]

From: [redacted]
Sent: 08 October 2008 14:44
To: [redacted]
Subject: Co-proxamol

Dear [redacted]

Thank you for your emails to the Department of Health about the withdrawal of co-proxamol.

The decision to withdraw co-proxamol from the market followed a full review of the risks and benefits. The MHRA/Commission on Human Medicines (CHM) does not make decisions based on cost or cost effectiveness – this is considered separately by the NHS and the National Institute for Health and Clinical Excellence (NICE).

Unfortunately your suggestion for different daily doses for patients depending on their body mass would not be practical. The critical dose is not dependent upon the size of the patient. The toxic dose of co-proxamol is close to the effective dose so decreasing the dose would not only decrease the risk of accidental overdose but would also decrease the benefit in terms of pain relief. Patients may then be tempted to take an extra dose in order to gain acceptable pain relief leading to an increased risk of overdose. Decreasing the dose would also not address the issue of increased toxicity of co-proxamol when taken with alcohol.

Finally you have suggested that the Department of Health/MHRA correspond directly with the medical defence organisations about co-proxamol. As medical defence organisations are independent of Government it would not be appropriate for the MHRA to comment on the cover provided by them for GPs who prescribe co-proxamol or any other unlicensed medicine. Individual GPs who have a concern over their indemnity cover should discuss this directly with the relevant organisation. The MHRA is not, however, aware that the Medical Defence Union (MDU) has issued advice to doctors advising against the use of co-proxamol. We understand that they have issued advice on the key issues which any doctor must consider before prescribing an unlicensed medicine.

The role of the MHRA is to monitor the risk: benefit balance of medicines and take appropriate regulatory action to safeguard public health as necessary. The clinical judgement to prescribe an unlicensed medicine to meet an individual patient's need is a matter for the individual prescriber.

I am sorry but there is no further advice I can give you on this matter.

Yours sincerely

[redacted]

From: [redacted]
Sent: 26 September 2008 17:27
To: [redacted]
Cc: [redacted]
Subject: RE: Response to your Query : [redacted] - Co-proxamol

From: [redacted]
Sent: 26 September 2008 14:56
To: [redacted]
Subject: Response to your Query : [redacted] - Co-proxamol

Our ref [redacted]

Dear [redacted]
Thank you for your email of 3 September to the Department of Health about the withdrawal of co-proxamol.
I understand an official from the Medicines and Healthcare products Regulatory Agency has replied to you directly and I hope your query has now been answered.
Yours sincerely,
[redacted]

No, you will see from the following correspondence and my reply that the position for up to 60000 pateints remains unsatisfactory except where some GPs and practices are ignoring the advice of the MDU and prescribing at great risk to themselves, leading to a postcode lottery.

What I was suggesting to you at the DoH is that the MHRA should be "called to order" in this instance for ignoring best medical practice: "pain medication should be tailored to each patient's individual need". They based their decision on a cost\benefit analysis done long ago for the average patient and not for each individual patient. MHRA should be asked to re-licence co-proxamol with amplified package warnings. In this context, if this drug is so dose-critical there should **surely** be different recommended daily dose for different body mass patients. This factor should be part of the package warning amplification.

[redacted]

From: [redacted]
Sent: 24 September 2008 16:39
To: [redacted]
Subject: [redacted]

Dear [redacted]

Thank you for your email to [redacted] in the [redacted] about the withdrawal of co-proxamol. As the Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for medicines licensing in the UK I have been asked to respond.

Following a full review of the risks and benefits of co-proxamol, the Committee on Safety of Medicines (CSM) determined that there was no evidence of a benefit of co-proxamol over paracetamol but that co-proxamol was much more dangerous than paracetamol in overdose. Therefore the risks of co-proxamol clearly outweighed the benefits. As the MHRA is legally bound to operate a licensing system based on the quality, safety and effectiveness of medicines, appropriate regulatory action had to be taken to cancel the licences for these products. On the other hand the benefit:risk balance for tricyclic antidepressants remain favourable which means that the benefits of these medicines outweigh the risk of serious adverse reactions even in overdose. All drugs are monitored under the Yellow Card Scheme which is used to collect information from health professionals and patients on suspected adverse drug reactions. The MHRA continues to monitor the benefit:risk ratio of all medicines.

As stated in previous correspondence, we do recognise that there are some patients who have not been able to find a suitable alternative to co-proxamol and therefore continued use of unlicensed co-proxamol for these patients is still possible if the doctor considers it to be in their best interest. This provision is set out in medicines legislation and is not an unusual arrangement although we do understand that use of this provision varies across the UK as it depends on individual prescribers taking responsibility for this.

Health Ministers have made a final decision to withdraw co-proxamol from the market. I am

[redacted]y but there is no further advice I can give you on this matter.

Yours sincerely

[redacted]

There is no question that for me, and for up to 60000 others co-proxamol works whereas paracetamol is useless at twice the dose. We would provide the evidence but were not asked. The CSM was WRONG and is depriving thousands of proper pain management.
Pain managers will tell you pain management should be tailored to the individual.
Let the MHRA continue to monitor the ridiculous and paradoxical situation they have caused. They have no remit to make a "final decision".

[redacted]

[redacted]

From: [redacted]
Sent: 24 September 2008 16:39
To: [redacted]
Subject: [redacted]

Dear [redacted]

Thank you for your email to [redacted] in the Department of Health about the withdrawal of co-proxamol. As the Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for medicines licensing in the UK I have been asked to respond.

Following a full review of the risks and benefits of co-proxamol, the Committee on Safety of Medicines (CSM) determined that there was no evidence of a benefit of co-proxamol over paracetamol but that co-proxamol was much more dangerous than paracetamol in overdose. Therefore the risks of co-proxamol clearly outweighed the benefits. As the MHRA is legally bound to operate a licensing system based on the quality, safety and effectiveness of medicines, appropriate regulatory action had to be taken to cancel the licences for these products. On the other hand the benefit:risk balance for tricyclic antidepressants remain favourable which means that the benefits of these medicines outweigh the risk of serious adverse reactions even in overdose. All drugs are monitored under the Yellow Card Scheme which is used to collect information from health professionals and patients on suspected adverse drug reactions. The MHRA continues to monitor the benefit:risk ratio of all medicines.

As stated in previous correspondence, we do recognise that there are some patients who have not been able to find a suitable alternative to co-proxamol and therefore continued use of unlicensed co-proxamol for these patients is still possible if the doctor considers it to be in their best interest. This provision is set out in medicines legislation and is not an unusual arrangement although we do understand that use of this provision varies across the UK as it depends on individual prescribers taking responsibility for this.

Health Ministers have made a final decision to withdraw co-proxamol from the market. I am sorry but there is no further advice I can give you on this matter.

Yours sincerely

[redacted]

Text of [redacted]

I note your response to my emails. How can you say there is nothing the DoH can add?

Suicides will happen whatever. Up to 60000 patients are now being denied their personal optimal pain solution. This is patently disproportionate.

No such precipitate action has be taken by MHRA concerning the even bigger killer, tri-cyclic anti depressants, also dangerous and life-threatening.

Co-proxamol was never freely administered into the public, it was on prescription only, with full package leaflet instructions on handling.

As a result of the MHRA action many people have now found that co-proxamol can be obtained off prescription on-line & with no such controls.

The whole emphasis in modern pain control is on tailoring the relief to the genetic and environmental factors affecting each individual patient.

The MHRA action flies in the face of this principle.

Moreover it conflicts, in practice, with the DoH response of 11th March For patients who are finding it difficult to change to an alternative to co-proxamol, for example when alternatives appear not to be effective or suitable, there is a provision in law for the supply of unlicensed co-proxamol on the NHS"

What is this Provision in Law? It is not apparent to the GPs in my practice nor to their medical insurers or the MDU who will not allow prescribing un-licensed drugs.

How can you say there is nothing the DoH can addwhilst this paradoxical conflict situation still remains? Some GPs are risking their careers to help patients.

Do not use the excuse of "clinical judgement". Clinical judgement for the last 20 years was that co-proxamol was safe and useful despite its suicide use.

Can the Department not bring the Agency to account? Who is the boss?

Prof Breckenridge was less than helpful to the Parliamentary Select Committee during the Seroxat affair. [redacted] defence did not impress the US court.

Maybe somebody less secretive about the Agency's motivations should be given an opportunity in the chair and to licence medicines.

Patient-led care is surely The Mission.

I explained the situation, personally, to the local MP last week and he has promised to take further action when the House reconvenes.

Pressure will not go away until the de-licensing is reversed.

Do not try to placate me again, - pass this up to your boss &c..

[redacted]

[redacted]

Thank you for your emails of 5 and 12 August to the Department of Health about the withdrawal of the painkiller co-proxamol.

Co-proxamol is a potentially dangerous and life threatening drug and can no longer be administered freely into the public. I trust you will appreciate the Government's position in that it is responsible for public safety.

I note that you written several times before about this issue. I am sorry that you were unhappy with previous responses. However, the information given to is the most up-to-date and accurate available, and there is nothing further the Department can add to this. The Government's position remains as set out in our latest reply dated 11 March.

Yours sincerely,

[redacted]

From: [redacted]
Sent: 15 August 2008 14:48
To: [redacted]
Cc: [redacted]
Subject: ACTION: FOI 08/301 - FOI Mclean co-proxamol letters

Importance: High

Attachments: [redacted]ugust 1.txt; [redacted]ugust 2.txt

Dear [redacted]

This is a Freedom of Information Request (Ref: FOI 08/301). The deadline for reply is 2nd September 08.

Please see the FOI section on Insite for the SOP including templates to use for replies.

Pleaser remember to send copies of replies to [redacted] and [redacted]

Additionally please remember to use a copyright statement in your reply if data and documents are supplied. The FOI section on Insite contains wording on this.

Many thanks

[redacted]

-----Original Message-----
From: [redacted]
Sent: 15 August 2008 11:34
To: [redacted]
Cc: [redacted]
Subject: FOI Mclean co-proxamol letters

Hello

I have spoken to [redacted] can these 2 emails please be logged as one FOI from [redacted] and allocated to me.

Thanks

[redacted]

[redacted]

[redacted]
From: [redacted]
Sent: 02 September 2008 16:57
To: [redacted]
Subject: Responses to FOI requests 08/300 & 301

Attachments: 08-236 - RM.pdf; 08-219 - RM.pdf; Response documents - RM.pdf

Dear [redacted]

I am writing in response to your recent FOI requests which were being handled by [redacted] I have learned that [redacted] has, unfortunately, been unavoidably absent for several days and so I am replying on his behalf.

In order that you are not kept waiting beyond the 20 working day period set out in the Act, I am responding to you electronically. However, I am aware that you have expressed a preference for a hard-copy reply, and I will be placing this in the post for you also (PDF hard copies).

Best regards

[redacted]

[redacted]

08/300

Your request:

"1. Please can you supply me with a copy of the complete question and response documents, appropriately redacted, for your FOI File reference 08/219 (Contact email addresses etc).

2. Please can you supply me with a copy of the complete question and response documents, appropriately redacted, for your FOI File reference 08/236 (Estate Policies etc).

3. Please can you supply me with a copy of the complete question and response documents, appropriately redacted, for your FOI File reference 08/126 (Seroxat etc). Please accept my request as pending. That is pending the resolution of your own file. For the avoidance of doubt, I do not require this request to be accepted by you in terms of the statutory FOI 20 day ruling until the "Result" column of your "MHRA FOI Disclosure List" signals from "Pending" to either "Answered" or "Refused". Thankyou.

4. Confirmation copy documentation held by and confirming your chairman, Dr Breckenridge has received my question on whether he accepts that the MHRA Coproxamol "Named Patient" policy has collapsed as a result of the MDDUOS document referred to at: http://www.mddus.com/mddus/2637.html

5. Copy documentation from your chairman, Dr Breckenridge to all aprties other than myself, of faxes, emails and letters, along with contemporaneous notes and minutes of any meetings that Dr Breckenridge has made in connection to my question on whether he accepts that the MHRA Coproxamol "Named Patient" policy has collapsed as a result of the MDDUOS document referred to at: http://www.mddus.com/mddus/2637.html"

MHRA reply

Points 1 & 2: Please find the relevant PDF files attached:


08-236 - RM.pdf (32 KB)


08-219 - RM.pdf (311 KB)

Point 3: Will be answered in due course

Points 4 & 5: Sir Alasdair's office has provided the following responses

Point 4. "We can confirm that Sir Alasdair's office has received the documentation but Sir Alasdair has been away from the Agency since 4 August on business and annual leave. He has now returned and has noted the contents of your letter."

Point 5. "As Alasdair Breckenridge has just returned from annual leave, we can confirm that no correspondence has been generated by him in connection with your question"

08/301

Your request:

"Thankyou for sending the information that I recently requested surrounding letters, faxes and emails that the MHRA have received on the subject of the Coproxamol ban.

Whilst studying the correspondence that the MHRA have received it has become evident that the enquiries only show one half of the picture.

Consequently, in terms of the Freedom of Information Act, please can you send me:-

Copies of the replies, appropriately redacted, that the MHRA have sent out in response to enquiries, letters, faxes and emails on the subject of the MHRA ban on Coproxamol?" on 3 Agust clarified to 1 Jan 2008 - 31 July 2008

MHRA reply