ANNEX 5

Annex 5

Review of Benefits and Risks for dextropropoxyphene-containing medicines provided by Medsafe

Report prepared by [redacted] Medsafe, November 2009.

1.0 PURPOSE

The purpose of this annex is to present an analysis of the benefits and risks of medicines containing dextropropoxyphene. The New Zealand approved medicines are Capadex and Paradex. These medicines are part funded by PHARMAC and are scheduled as class C5 controlled drugs.

This report includes:

- A review of published data on efficacy and safety
- New Zealand spontaneous adverse reaction data
- New Zealand Poisons Centre data
- A summary of a medicine utilisation study for Paradex
- A summary of relevant discussions by the UK and US Regulators.

It should be noted that the review of the published literature is not exhaustive; it is provided by Medsafe to provide background information for the Committee on the efficacy and safety of dextropropoxyphene-containing medicines. The intention is for the review to help inform the Committee's discussions on the balance of benefits and risks for these medicines.

NOTE: Medicines containing a combination of dextropropoxyphene and paracetamol are known as co-proxamol in the UK. Dextropropoxyphene is known as propoxyphene in the US.

2.0 EXPOSURE

Usage data has been provided by PHARMAC.

Table 1: Estimated number of patients taking dextropropoxyphene-containing products.

	2005	2006	2007	2008	2009
Capadex	4108	3655	3332	2889	2491
Paradex	101284	90617	88512	83700	75830
Total	**104,927**	**93,876**	**91,528**	**86,309**	**78,099**

Comments

There appears to have been a steady decline in use since the last MARC review and regulatory action which started in 2005.

3.0 PHARMACOKINETICS

3.1. Absorption

Following oral administration, the hydrochloride and napsylate salts of dextropropoxyphene are absorbed in the small intestine. The napsylate salt is more slowly absorbed than the hydrochloride salt. There are, however, no significant differences in oral bioavailability between the hydrochloride and napsylate salts[1].

Barkin et al. 2006[1] state the oral bioavailability ranges from 30-70%. Perrier & Gibaldi 1972[2] report that the mean systemic availability of dextropropoxyphene after oral administration (8 subjects)

[1] Barkin RL, Barkin SJ and Barkin DS 2006 'Propoxyphene (dextropropoxyphene): A critical review of a weak opioid analgesic that should remain in antiquity' Am J Therap 13: 534-542.

was 18% at 65 mg and 28% at 130 mg. At higher doses (i.e. 195 mg) only a modest increase in bioavailability (to 33%) was observed.

The influence of food (empty stomach, high carbohydrate, high fat, and high protein meals) on the pharmacokinetics of dextropropoxyphene following a single dose of 130 mg was investigated by Welling et al. 1976[3]. Similar pharmacokinetic profiles were observed for dextropropoxyphene and norpropoxyphene when dextropropoxyphene was administered on an empty stomach and with food. An exception was observed for the C_{max} following a high carbohydrate meal which was significantly increased relative to administration on an empty stomach and administration following high fat and high protein meals.

3.2. *Distribution*

Plasma protein binding is high. The time to peak concentration is 2 to 2.5 h and peak plasma concentration is 0.05 to 0.1 µg/mL with a volume of distribution (Vd) of 12-26 L/kg[2].

3.3 Elimination

3.3.1 Metabolism

The major pathway for the metabolism of dextropropoxyphene is *N*-demethylation in the liver to norpropoxyphene. Other minor metabolic pathways include further *N*-demethylation (to dinordextropropoxypehene), aromatic hydroxylation (with subsequent conjugation), and ester hydrolysis.[9] Perrier & Gibaldi 1972[2] report dextropropoxyphene undergoes significant first-pass metabolism in the liver, and suggest that extrahepatic metabolism may also occur. The major cytochrome P450 (CYP) enzyme involved in the metabolism of dextropropoxyphene is CYP34A.[4] Dextropropoxyphene is both a substrate and an inhibitor of CYP2D6.

Dextropropoxyphene has a half-life ($T_{1/2}$) of 6-12 h.[6] Flanagan et al 1989[5] found the mean $T_{1/2}$ increased significantly to 22 h following repeat dosing (65 mg TID, 1 week) in young subjects (21-28 years).

In contrast, the $T_{1/2}$ of paracetamol is 1-4 h.

3.3.2 Excretion

Renal excretion is the major pathway for norpropoxyphene elimination.

3.4 Pharmacokinetics of metabolites

Norpropoxyphene has a $T_{1/2}$ of 30-36 h. The median $T_{1/2}$ did not increase after multiple dosing with norpropoxyphene in young or elderly subjects. The $T_{1/2}$ for norpropoxyphene correlated with estimated creatinine clearance[5].

3.5 Consequences of possible genetic polymorphism

Somogyi et al. 2004[9] found no difference in the pharmacokinetics of six CYP2D6 extensive metabolisers and one poor metaboliser of dextropropoxyphene and norpropoxyphene in an *in vitro* study using human liver microsomes.

3.6 Dose proportionality and time dependency

No data available.

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[2] Perrier D & Gibaldi M 1972 'Influence of first-pass effect on the systemic availability of propoxyphene' J Clin Pharmacol New Drugs 12(11): 449-53.
[3] Welling PG et al. 1976 'Propoxyphene and norpropoxyphene: influence of diet and fluid on plasma levels' Clin Pharmacol Ther 19: 559-65.
[4] Somogyi AA, Menelaou A & Fulliston SV 2004 'CYP3A4 mediates dextropropoxyphene N-demethylation to nordextropropoxyphene: human in vitro and in vivo studies and lack of CYP2D6 involvement' Xenobiotica 34: 875-7.
[5] Flanagan RJ, Johnston A, White AST & Crome P (1989) 'Pharmacokinetics of Dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dosage' Br J Clin Pharmac 28: 463-9.

3.7 Intra- and inter-individual variability

Perrrier & Gibaldi[2] report significant variations in the systemic availability of dextropropoxyphene between individuals. At an oral dose of 65 mg dextropropoxyphene (8 subjects) the systemic availability ranged between 8% and 24%. Intra-individual variability was remarkably low.

3.8 Pharmacokinetics in target population

3.8.1 Impaired renal function

Bailie et al 2002[6] report accumulation of norpropoxyphene can occur in dialysis patients. There is some evidence that norpropoxyphene clearance is reduced in dialysis patients. Gaicomini et al 1980[7] found that after a 130 mg dose, the area under the curve (AUC) was on average 76% greater in anephric patients and C_{max} was increased by 89% relative to normal healthy volunteers. A small increase was observed in the C_{max} (by 26%) for norpropoxyphene, but consistent with the fact that the kidney is the major route of excretion for norpropoxyphene, the AUC was significantly increased (by 56%) for the major metabolite, norpropoxyphene. Flanagan et al. 1989 found the $T_{1/2}$ for dextropropoxyphene correlated with estimated creatinine clearance. The FDA at their Advisory Committee meeting in 2009 considered the change in pharmacokinetics depended on the degree of renal impairment.

3.8.2 Impaired hepatic function

Dextropropoxyphene is extensively metabolised by the liver; it is therefore reasonable to expect that in hepatic impairment the pharmacokinetics of dextropropxyphene and norpropoxyphene may be altered. Giacomini et al. 1980[8] found significant increases in the C_{max} (by 199%) and AUC (by 93%) of dextropropoxyphene following a single dose of dextropropoxyphene in patients with hepatic cirrhosis (severity of cirrhosis unknown) compared with subjects with normal hepatic function. Correspondingly, significant decreases in C_{max} (by 72%) and AUC (by 73%) were observed in the major metabolite norpropoxyphene.

3.8.3 Gender effects

Flanagan et al. 1989[9] found no significant differences in the median $T_{1/2}$ of dextropropoxyphene between male and female subjects following a single dose (65 mg) or multiple doses (65 mg, TID for 1 week).

3.8.4 Race

No data available.

3.8.5 Weight

No data available.

3.8.6 Effects in the Elderly

Flanagan et al. 1989[9] found the median $T_{1/2}$ of dextropropoxyphene in elderly subjects (70-79 years old) was 172% higher than young subjects (21-28 years old) after a single dose (65 mg) of dextropropoxyphene. The C_{max} and AUC were also significantly higher (by 164% and 175% respectively) compared with young subjects. Similar results were found with multiple doses (65 mg, TID for 1 week).

The C_{max} was unaltered for norpropoxyphene following a single dose of dextropropoxyphene but the $T_{1/2}$ was increased by 84% in elderly subjects.

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[6] Bailie GR, Johnson CA (2002) 'Safety of Propoxyphene in dialysis patients' Semin Dial 15(5): 375-6.
[7] Giacomini et al 1980 'Effect of hemodialysis on propoxyphene and norpropoxyphene concentrations in blood of anephric patients' Clin Pharmacol Ther 27: 508-14.
[8] Giacomini et al 1980 ' Propoxyphene and norpropoxyphene plasma concentrations after oral propoxyphene in cirrhotic patients with and without surgically constructed portacaval shunt Clin Pharmacol Ther 28: 417-424.
[9] Flanagan RJ, Johnston A, White AST & Crome P (1989) 'Pharmacokinetics of Dextropropoxyphene and nordextropropoxyphene in young and elderly volunteers after single and multiple dosage' Br J Clin Pharmac 28: 463-9.

The frequency of dosing influences pharmacokinetic parameters in the elderly. In the Flanagan et al. 1989[9] study, following multiple dosing with dextropropoxyphene in elderly subjects, the C_{max} for dextropropoxyphene increased by 53% relative to a single dose, but the $T_{1/2}$ was unchanged. For norpropoxyphene, the C_{max} was significantly higher (by 470%) relative to single dose, whereas the $T_{1/2}$ was unchanged.

3.8.7 Effects in Children

No data available.

3.9 Pharmacokinetic interactions

3.9.1 In vitro studies

Dextropropoxyphene inhibits CYP2D6 mediated metabolism of dextromethorphan and desmethylimipramine *in vitro* in human liver microsomes.

3.9.2 In vivo studies

While it was considered for a long time that other medicines using CYP2D6 for their metabolism may lead to toxic levels of the substrate, more recent findings of Somogyi et al. 2004[4] implicate CYP3A4 as the main target for pharmacokinetic interactions.

FDA, at its Advisory Committee meeting in January 2009, considered drug-drug interactions involving CYP34A inducers and inhibitors required close attention. Strong CYP3A4 inhibitors such as clarithromycin, HIV protease inhibitors, ketoconazole, and grapefruit juice can cause an increase in norpropoxyphene levels. It was also stated that CYP3A4 inducers such as carbamazepine and rifampicin can induce CYP3A4 and decrease levels of norpropoxyphene. The fact that CYP3A4 is the major enzyme involved in the metabolism of several drugs was highlighted as having greater potential for drug-drug interactions [in comparison with CYP2D6 which was originally thought to be the main CYP in dextropropoxyphene metabolism]. Published case reports describe pharmacokinetic interactions e.g. with carbamazepine[10,11].

Ferner et al. 1998[12], in a review of the interaction between alcohol and medicines, report that significant effects from acute ethanol ingestion have been demonstrated with dextropropoxyphene in healthy volunteers; the bioavailability of a single oral dose was increased by an average of 25%, although this was not found to significantly alter the subjects' performance on objective tests of psychomotor and cognitive function. However, a small pharmacokinetic interaction study (n=6) did not show a pharmacokinetic interaction of dextropropoxyphene with alcohol.[13]

Comment

The potential for norpropoxyphene accumulation with repeat dosing is apparent from its longer half-life relative to dextropropoxyphene, particularly in renal and hepatic impairment and in the elderly.

It has only recently become apparent that the major route for the metabolism of dextropropoxyphene is catalysed by hepatic CYP3A4 to norpropoxyphene. Although only limited substantive evidence exists there is significant potential for pharmacokinetic interactions to occur with CYP34A inhibitors and inducers.

The MARC may consider that the interactions section of the data sheets for Paradex and Capadex need revising based on this information.

[10] Yu YL, Huang HD, Woo CE & Chang CM 1986 'Interaction between carbamazepine and dextropropoxyphene' Postgraduate Medical Journal 62: 231-33.
[11] Allen S 1994 'Cerebellar dysfunction following dextropropoxyphene-induced carbamazepine toxicity' Postgrad Med 70: 764-69.
[12] Ferner RE 1998 'Interactions between alcohol and drugs' Adverse Reactions Bulletin 189: 719-21.
[13] Seller EM, Hamilton CA, Kaplan HL, Neema C, Degani NC & Foltz RL 1985 'Pharmacokinetic interaction of propxocyphene with ethanol' Br J Clin Pharmac 19: 398-401.

4.0 PHARMACODYNAMICS

4.1 Mechanism

Dextropropoxyphene binds to the opioid receptors in the central nervous system. More specifically, it is an open chain μ-opioid receptor agonist which also acts as a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist.[14] Dextropropoxyphene has a higher affinity for the μ-opioid receptor than the δ-opioid and κ-opioid receptors. Rang et al 1999[15] state dextropropoxyphene is referred to as a weak agonist because the maximal effects, analgesic and unwanted, are less than that of morphine.

4.2 Primary pharmacology

Dextropropoxyphene is an analgesic opioid. Analgesic effects occur within 30 to 60 mins, peak within 120 mins, and persist for up to 6 h[15].

4.3 Secondary pharmacology

The secondary pharmacology of dextropropoxyphene is not well described. However, it produces other CNS effects similar to those seen with other morphine-like opioids[16] and adverse effects (such as sedation, respiratory depression, reduced gastrointestinal motility, euphoria, and rashes) consistent with other μ-opioid receptor agonists.

4.4 Relationship between plasma concentration and effect

Barkin et al. 2006[1] report that the reference ranges of dextropropoxyphene vary, but one that is frequently seen is a therapeutic range in adults of 0.1-0.4 μg/mL.

4.5 Pharmacodynamic interactions

Ferner et al. 1998[12] consider that the interaction between ethanol and dextropropoxyphene may in part be due to an increase in the bioavailability of dextropropoxyphene but, in addition, that the respiratory depression that both agents cause is likely to be additive.

4.6 Genetic differences in pharmacodynamic response

Somogyi et al. 2004[4] consider variability in the pharmacodynamics of dextropropoxyphene to be more likely to be attributable to inter-individual variability in CYP3A4 expression and/or drug-drug interactions (rather than CYP2D6-related).

5.0 CLINICAL EFFICACY

Dextropropoxyphene and dextropropoxyphene/paracetamol combinations were developed in the 1950s and 1960s and have therefore not been required to demonstrate the same level of clinical efficacy as would be required for a new medicine approved today. For example, in the US the first dextropropoxyphene products were approved in 1957 on the basis of safety data only.

5.1 Dose-response studies

Beaver 1984[17] reviewed dose-response studies for dextropropoxyphene HCl (32-200 mg) and dextropropoxyphene napsylate (50-300 mg). Three studies were designed to determine the relative potencies of the napsylate and hydrochloride salts. These studies confirm a positive dose-response curve for dextropropoxyphene, with relative potencies of the napsylate to hydrochloride salt of 0.64 and 0.83 reported for postpartum uterine cramp pain (mean analgesia score) and postoperative and fracture pain (SPID), respectively. If bioavailability of the two salts were

[14] Silva-Moreno A, Lopez-Munoz FJ & Cruz SL 2009 'D-propoxyphene and dipyrone co-administration produces greater antinociception and fewer adverse effects than single treatment in rats' European Journal of Pharmacology 607: 84-90.
[15] Rang HP, Dale MM & Ritter JM Pharmacology. 4th Ed Harcourt, Brace and Company, London. 1999
[16] Committee on Safety of Medicines, Subcommittee on Pharmacovigilance 2004 Risk-Benefit of Co-proxamol products CSM/04/8/5p
[17] Beaver WT 1984 'Analgesic efficacy of dextropropoxyphene and dextropropoxyphene-containing combinations: a review' Human Toxicol 3: 191S-220S.

identical, the napsylate salt would be 0.66 times as potent as the hydrochloride in analgesic effect (based on relative molecular weights of the two salts).

Comment

This is the most recent published review of dose response that could be found by Medsafe. The studies included in the review were performed before the 1980s. The number of patients included appeared to be around 50 per treatment. There is no objective measurement for pain; such measurements are inherently subjective. In this review, relative potency was estimated by the sum of the pain intensity differences (SPID) or mean analgesia score. SPID is a validated method for determining clinically important changes in acute pain outcomes with an estimated threshold of 2. This threshold was exceeded at all doses assessed. It is unclear whether mean analgesia score is a validated method.

5.2 Published clinical efficacy profile

Capadex and Paradex are indicated for the relief of chronic pain of moderate severity. The data sheets for these medicines do not contain clinical study data in support of clinical efficacy.

5.3 Systematic reviews of clinical efficacy

5.3.1 Cochrane Database Review (2008)[18]

This systematic intervention review was first published in 1999, and updated in 2008. The primary objective of the review was to determine analgesic efficacy and adverse effects of single dose oral dextropropoxyphene alone and in combination with paracetamol for moderate to severe postoperative pain. A second objective was to compare the results with other analgesics assessed in the same way to provide evidence-based recommendations for clinical practice.

Eleven studies were identified from 1954 to 1994 that met the inclusion criteria; 6 studies (440 subjects) compared dextropropoxyphene with placebo, 4 studies (325 subjects) and one individual patient meta-analysis (638 subjects) compared dextropropoxyphene plus paracetamol with placebo.

For a single dose of dextropropoxyphene 65 mg in post-operative pain the number needed to treat (NNT) for at least 50% pain relief was 7.7 (95%CI 4.6-22) when compared with placebo over 4-6 h. There was no significant difference between the proportion of participants re-medicating within 4 to 8 h with dextropropoxyphene 65 mg (35%) and placebo (43%), relative risk 0.8 (95% CI 0.7-1.03).

For the equivalent dose of dextropropoxyphene combined with paracetamol 650 mg the NNT was 4.4 (95%CI 3.5-5.6) when compared with placebo. Significantly fewer participants re-medicated within 4-8 h (34%) than with placebo (57%), relative risk 0.7 (95%CI 0.5-0.8).

These results were compared with those for other analgesics obtained from equivalent systematic reviews. The authors concluded the combination of dextropropoxyphene 65 mg with paracetamol 650 mg shows similar efficacy to tramadol 100 mg for single dose studies in post-operative pain (but with a lower incidence of adverse effects). The same dose of paracetamol combined with 60 mg codeine appeared more effective; however, because of a slight overlap in the 95% CI the authors considered this was not a robust conclusion. Ibuprofen (400 mg) was concluded as having a lower (better) NNT than both dextropropoxyphene 65 mg plus paracetamol 650 mg, and tramadol 100 mg.

The authors concluded that single dose dextropropoxyphene on its own is not particularly effective in relieving post-operative pain. The results of the review support the view that dextropropoxyphene used in combination with paracetamol provides more effective analgesia than placebo, but ibuprofen (400 mg) provides better analgesia than the dextropropoxyphene/paracetamol combination.

[18] Moore RA, Collins S, Rees J, Derry S & McQuay HJ (2008) Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. Cochrane Database of Systematic Reviews.

The authors considered a method needs to be developed to quantitatively assess efficacy in prolonged usage.

An analysis comparing dextropropoxyphene 65 mg with placebo using the number of patients experiencing at least 50% pain relief to determine efficacy is given below.

Analysis 1.1. Comparison 1 Dextropropoxyphene HCl 65mg Vs Placebo, Outcome 1 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR).

Review: Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 1 Dextropropoxyphene HCl 65mg Vs Placebo

Outcome: 1 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Berry 1975	26/73	18/76		30.0 %	1.50 [0.90, 2.50]
Bloomfield 1980	21/25	19/25		32.2 %	1.11 [0.84, 1.46]
Cooper 1986	16/50	10/56		16.1 %	1.79 [0.90, 3.58]
Coutinho 1976	8/15	6/15		10.2 %	1.33 [0.61, 2.91]
Trop 1979	9/25	1/25		1.7 %	9.00 [1.23, 65.85]
Van Steden 1971	5/26	6/29		9.7 %	0.93 [0.32, 2.69]
Total (95% CI)	**214**	**226**		**100.0 %**	**1.48 [1.15, 1.90]**

Total events: 85 (Treatment), 60 (Placebo)

Heterogeneity: Chi² = 8.40, df = 5 (P = 0.14); I² =40%

Test for overall effect: Z = 3.01 (P = 0.0026)

0.1 0.2 0.5 1 2 5 10

Favours placebo Favours treatment

The corresponding analysis for dextropropoxyphene 130 mg is given below.

Analysis 2.1. Comparison 2 Dextropropoxyphene HCl 130 mg Vs Placebo, Outcome 1 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR).

Review: Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 2 Dextropropoxyphene HCl 130 mg Vs Placebo

Outcome: 1 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Trop 1979	10/25	1/25		100.0 %	10.00 [1.38, 72.39]
Total (95% CI)	**25**	**25**		**100.0 %**	**10.00 [1.38, 72.39]**

Total events: 10 (Treatment), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 2.28 (P = 0.023)

0.01 0.1 1 10 100

Favours placebo Favours treatment

The corresponding analysis comparing dextropropoxyphene 65 mg plus paracetamol 650 mg with placebo is given below.

Analysis 3.1. Comparison 3 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo, Outcome 1 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR).

Review: Single dose oral dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain

Comparison: 3 Dextropropoxyphene HCl 65mg + Paracetamol 650mg Vs Placebo

Outcome: 1 No. patients experiencing at least 50% pain relief (>50% maxTOTPAR)

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cooper 1980	14/40	11/48		12.7 %	1.53 [0.78, 2.99]
Cooper 1981	24/42	6/37		8.7 %	3.52 [1.62, 7.67]
Evans 1982	15/30	8/30		10.9 %	1.88 [0.94, 3.75]
Menig 1981	17/50	9/48		12.5 %	1.81 [0.90, 3.67]
Moore 1997	114/316	40/322		54.1 %	2.90 [2.10, 4.02]
Total (95% CI)	**478**	**485**		**100.0 %**	**2.52 [1.99, 3.20]**
Total events: 184 (Treatment), 74 (Placebo)					
Heterogeneity: Chi² = 5.14, df = 4 (P = 0.27); I² =22%					
Test for overall effect: Z = 7.59 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours placebo Favours treatment

5.3.2 Meta-analysis by Po & Zhang (1997)[19]

This analysis included 26 double-blind randomised controlled trials of dextropropoxyphene-paracetamol, paracetamol, and placebo. The study subjects were adults with post-surgical pain and treated with single oral dose dextropropoxyphene-paracetamol, paracetamol alone or placebo. Dextropropoxyphene alone was not included in these trials.

The outcome measures assessed were sum of difference in pain intensity (SPID) from baseline, the response ratio (response defined as moderate to excellent pain relief), and response rate ratio.

Of the 27 eligible trials:

- 21 were two-armed placebo controlled trials; 6 of these were dextropropoxyphene-paracetamol versus placebo, the remainder were paracetamol compared with placebo.
- 6 were three-armed placebo controlled trials comparing dextropropoxyphene-paracetamol against placebo.
- 25 trials were single dose comparisons; 2 trials were multiple dose (up to 48 h).
- The type of pain related to: episiotomy, postpartum, arthritis, tooth extraction, oral surgery, post-surgical, caesarean, orthopaedic, and musculoskeletal disorders.

Two different comparisons were made: a head-to-head comparison for the three-arm studies, and an indirect comparison for the two-arm studies. Results for the SPID analysis are shown in the figure below.

[19] Po ALW & Zhang WY 1997 'Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol' BMJ 315: 1565-71.

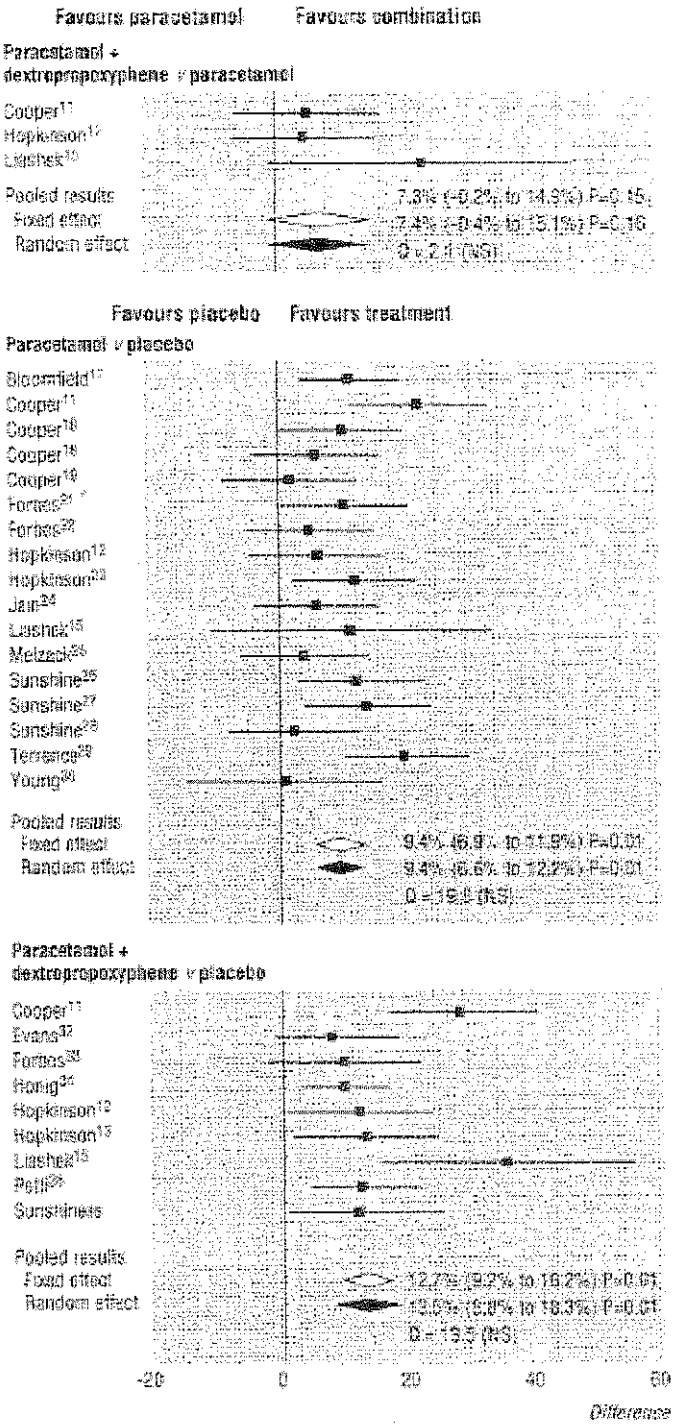

Fig 1 Mean (95% confidence interval) differences in percentage sum of differences in pain intensity between treatments

The results from head-to-head comparisons indicated both dextropropoxyphene plus paracetamol, and paracetamol alone, were efficacious compared with placebo on the basis of the sum of pain intensity difference (SPID) and the response rate ratio. There was however no statistically significant difference detected in these parameters between the two treatment groups, although a trend favouring combination was apparent in the three head-to-head studies included in the SPID analysis (see figure below).

Pooled data from the indirect comparisons also showed the dextropropoxyphene plus paracetamol combination and paracetamol alone were efficacious as determined by the SPID and response

rate ratios. Again, there was no statistically significant difference in efficacy between dextropropoxyphene plus paracetamol and paracetamol alone when determined against these parameters. A mean NNT of 4 was calculated for both the dextropropoxyphene/paracetamol combination and paracetamol alone to obtain moderate to excellent pain relief.

Comment

The meta-analyses support the efficacy of single doses of dextropropoxyphene-paracetamol combinations for the relief of moderate pain. However, this combination did not demonstrate superiority over paracetamol alone.

5.3.3 Other systematic reviews

Moore & McQuay[20] conducted a systematic review of single-patient data from double-blind randomised controlled trials in patients with moderate to severe pain after surgery or dental extraction to assess the effectiveness and safety of oral tramadol compared with standard analgesics. The dextropropoxyphene data from this review were incorporated into the Cochrane review described above and will not therefore be further discussed.

A qualitative systematic review by Goldstein & Turk 2005[21] examining the efficacy (and safety) of dextropropoxyphene in older patients (≥55 years) compared with other opioid analgesics retrieved nine studies involving predominantly older patients (>50%). Two trials included a placebo arm; the remaining studies included only comparator agents. The comparator agents in these studies included opiates and non-opiates (i.e. codeine, paracetamol, diflunisal, suprofen, meptazinol, diclofenac, dihydrocodeine, and morphine). The nine studies ranged from 1 day (single dose) to 24 weeks in duration and treatments were for a number of indications including arthritic pain, orthopaedic pain, joint pain, musculoskeletal pain, and terminal cancer. Table 2 provides a summary of the trials included in this review and the authors' assessments of efficacy. The authors considered that, overall, dextropropoxyphene appeared to provide pain relief equivalent to that of most comparator agents.

Comment

This qualitative review includes several small studies; five of the nine studies included less than 50 patients per treatment. Although many studies appear to be underpowered to detect small differences in efficacy, these studies taken together suggest that dextropropoxyphene alone or in combination is not superior to any of the other comparator treatments.

5.4 Published clinical studies

A number of single-dose clinical studies have investigated the efficacy of dextropropoxyphene alone or in combination with paracetamol; these studies have been considered in the systemic reviews described above.

The number of clinical studies investigating the use of repeat-dosing with dextropropoxyphene in chronic pain is limited. The available studies predominantly compare the efficacy of dextropropoxyphene (alone or in combination) with another analgesic (e.g. NSAID or another opioid) and are of limited duration. More recent studies in patients with osteoarthritic pain (Bossier et al 1992[22], Lloyd et al 1992[23]) and cancer pain (Mercadante et al 1998[24]) are briefly summarised below. These three studies were included in the Goldstein & Turk 2005[25] review described above.

[20] Moore RA & McQuay HJ (1997) 'Sgle-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics'Pain 69: 287-94.
[21] Goldstein DJ & Turk DC 2005 'Dextropropoxyphene. Safety and efficacy ion older patients' Drugs Aging 22(5): 419-32.
[22] Bossier Ch, Perpoint B, Laporte-Simitsidis S, Mismetti P, Hocquart J, Gayet JL, Rambaud C, Queneneau P & Decousus H 1992 'Acceptability and effeicay of two associations of paracetamol with a central analgesic (dextropropoxyphene or codeine) : comparison in osteoarthritis' J Clin Phamacol 32 : 990-5.

Table 2. Summary of trials included in the review of Goldstein & Turk (adapted from Goldstein & Turk, 2005)

Study (year)	Treatment groups (no. patients)	Design	Indication	Authors' qualitative assessment of efficacy
Boyle et al. (1960)	DPP HCl 65mg bid/qid (121) DPP HCl 32mg/ASA 325 mg bod/qid (121) Codeine 65mg (121) Codeine 32mg/ASA 325mg (121) Placebo (121)	Double-blind cross-over, 3-6 periods comparing 2 treatments of 5-7 days each with potential to repeat 3 times	Mixed	DPP 65mg significantly superior to placebo (p<0.01); DPP not significantly different from ASA 650 mg. DPP/ASA 325mg significantly superior to placebo (p<0.01); DPP 65mg/ASA 325mg not significantly different from DPP 65mg, ASA 650mg or codeine 65mg. Codeine 65mg statically significantly superior to DPP 65 mg (p<0.01) Codeine 32 mg/ASA 325 mg significantly superior to all other treatments.
Brooks et al. (1982)	DPP HCl 65mg (24) DPP HCl 65mg/APAP 650mg (24) DPP HCl 65 mg/ASA 650mg (24) APAP 650mg (24) ASA 650mg (24) Placebo (24)	Double-blind, single-dose, crossobver,1 week between treatments; add on to NSAID	Rheumatoid arthritis and osteoarthritis arthritis	No significant difference among treatments as add-on therapy to NSAID.
Rao & Sharma (1982)	DPP HCl 65mg/APAP 650mg qid (20) Diflunisal 500 mg bid (20)	Randomised, single-blind, parallel, 5 days	Mixed orthopaedic	No significant difference between treatments for spontaneous pain, night pain, patients' evaluation or clinicians' assessment. Diflunisal statistically superior for tenderness on days 2 and 3 and for pain on passive movement on days 4 and 5 (p<0.05).
Salzman & Brobyn (1983)	DPP 65mg qid (59) Suprofen 200mg qid (55)	Double-blind, parallel, 24 weeks	Musculoskeletal pain	No significant difference between treatments for pain intensity or relief.
Oro (1984)	DPP 65mg/APAP 650mg qid (32) Meptazinol 200mg qid (32)	Double-blind, crossover, 2 periods of 5 days each with 1 day placebo washout between	Mixed orthopaedic and arthritis	DPP/APAP and meptazinol statistically superior to placebo for spontaneous pain, pain on pressure, passive movement, and functional impairment. Meptazinol statistically significantly superior to DPP/APAP for overall assessment of effectiveness, functional improvement (p<0.05).
Parr et al (1989)	DPP 65mg/APAP 650mg qid (382) Diclofenac 100mg SR od (373)	Double-blind, parallel, 4 weeks	Joint pain	No significant difference between treatment groups in pain by questionnaire. Diclofenac significantly superior to DPP/APAP for VAS pain (p<0.05).
Bossier et al (1992)	DPP 60mg/APAP 800mg tid (70) Codeine 60mg/APAP 1000mg tid (71)	Double-blind, parallel, 6 days	Osteoarthritis	DPP/APAP statistically superior to codeine/APAP for success rate (p=0.005). No significant difference between DPP/APAP and codeine/APAP for pain assessed by either VAS or verbal categorical scales or clinician assessment.
Llyod et al (1992)	DPP HCl 65mg/APAP 650mg tid/qid (43) Dihydrocodeine 60mg CR 1-2 bid (43)	Double-blind, parallel, 2 weeks	Hip osteoarthritis	No significant difference between treatments for mean or maximum pain by VAS or severity of joint pain.
Mercandante et al (1998)	DPP 120-240 mg/day (16) Morphine SR 20 mg/day (16)	Randomised, single-blind, parallel	Terminal cancer	No significant difference between treatments in pain by VAS.

APAP- paracetamol; ASA – aspirin; DPP – dextropropoxyphene; VAS- visual analogue scale.

[23] Lloyd RS, Costello F, Eves MJ, James IGV & Miller AJ 1992 'The efficiency and tolerability of dihydrocodeine tablets and combination dextropropoxyphene/paracetamol tablets in patients with severe osteoarthritis of the hips' Current Medical Research and Opinion 13(1): 37-48.

[24] Mercandante S, Salvaggio L, Dardanoni G, Agnello A & Garofalo S 1998 'Dextropropoxyphene versus morphine in opioid-naïve cancer patients with pain. Journal of Pain and Symptom Management 15(2): 76-81.

Bossier et al. 1992 examined the acceptability (patient tolerance) of multiple doses of dextropropoxyphene (30 mg) plus paracetamol (400 mg) capsules (6 capsules/day) compared with codeine (30 mg) plus paracetamol (500 mg) tablets (6 tablets/day) for 6 days in a double blind randomised controlled trial of 141 patients with active knee or hip osteoarthritis. Seventy-one patients were included in the codeine plus paracetamol arm, and 70 were in the dextropropoxyphene plus paracetamol arm. The baseline characteristics were not significantly different between the two treatment groups. A secondary endpoint was comparative analgesic efficacy, determined as visual and verbal pain scales and overall efficacy assessment by physician and patient at the end of the treatment period. No significant differences were detected between the two treatment arms in any of the efficacy parameters assessed.

Comment

This study was not primarily designed to investigate the comparative efficacy of dextropropoxyphene plus paracetamol with codeine for analgesia in patients with active osteoarthritis.

Lloyd et al. 1992[23] investigated the comparative efficacy and tolerability of dextropropoxyphene plus paracetamol and controlled-release dihydrocodeine in 86 patients with severe osteoarthritis of the hip in a double blind randomised control trial. Two dose regimens were used for each treatment arm based on whether patients were naïve to the treatment or not. Within-treatment comparisons were made of mean and maximum visual analogue pain scores, number of nights waking due to pain, pain on passive movement of worst affected joint, difference in severity of joint pain.

Twenty out of 43 of the patients in the dihydrocodeine arm and 9 out of 43 of the patients in the dextropropoxyphene plus paracetamol arm dropped out of the study, with side effects cites as the main reason for withdrawal.

The authors concluded that after two weeks of treatment, controlled-release dihydrocodeine provided superior analgesia to dextropropoxyphene plus paracetamol. Some within-group comparisons were made in this study. While a statistically significant decrease in the maximum and mean daily pain scores was observed between week 2 and week 1, no difference was detected in the dextropropoxyphene plus paracetamol group. Comparison of week 1 or week 2 with baseline visual analogue scores was not made.

For the frequency of 'nights waking because of pain' assessment, there was a statistically significant decrease in frequency of waking in week 2 versus week 1 in the dextropropoxyphene plus paracetamol group. Again, comparison of week 1 or week 2 with baseline waking was not made.

For the investigator assessments of severity of joint pain, statistically significant decreases were observed from week 2 to baseline and from week 3 to baseline for both arms of the study.

Comment

This study was designed to have 80% power at the 5% significance level to detect a 7.5% difference in the visual analogue pain scores between dextropropoxyphene and paracetamol in combination and controlled-release dihydrocodeine for analgesia in patients with severe osteoarthritis. The findings of this study support the superiority of controlled release dihydrocodeine over dextropropoxyphene/paracetamol.

Mercandante et al 1998[24] investigated the comparative efficacy of dextropropoxyphene with morphine in 32 advanced cancer patients with pain that was no longer responsive to non-opioid medicines in a single-blind randomised controlled trial. Patients with co-existing liver or renal disease were excluded from the study. Sixteen patients were administered either dextropropoxyphene (from 120-240 mg/day) or controlled-release morphine (16 patients) at 20 mg/day. Patients were permitted to switch from one treatment arm to the other during the study.

The mean dose of opioid was expressed as an equi-analgesic dose of morphine, and doses used were recorded during the first 10 days and the last 4 weeks of life. Primary tumours were heterogenous amongst the patients (i.e. lung, breast, urogenital, gastrointestinal, liver and pancreas, and others). Non-opioid medicines were continued during the trial, if not contraindicated.

Pain intensity, measured on the visual analogue scale was evaluated as one endpoint and assessments were also made of side effects and used to calculate a system distress score.

Thirteen patients switched to morphine from the dextropropoxyphene arm during the study, and three switched to dextropropoxyphene from the morphine treatment arm. Increased pain intensity was the reason cited for switching from dextropropoxyphene to morphine. Pain, as determined on the visual analogue scale, was not statistically different between the treatment arms.

The authors considered dextropropoxyphene produced visual analogue scores and symptom distress scores similar to those for the lowest doses of slow release morphine in the first 10 days of therapy. The authors considered the study results confirmed the role of weak opioids as a second step in the analgesic ladder in cancer pain. The data for the last 4 weeks of the study were not included in the paper.

Comment

This study was designed to investigate the efficacy of dextropropoxyphene for analgesia compared with morphine in patients with terminal cancer pain. It is difficult to interpret the findings of this study in light of the heterogeneity of cancer types and the small size of the study. Switching of 13 out of 16 patients from the dextropropoxyphene arm to the morphine arm during the study does, however, suggest superiority of morphine over dextropropoxyphene.

Bannwarth 1999[25] qualitatively reviewed studies of analgesic efficacy in chronic non-malignant nociceptive pain. This review included seven studies with a dextropropoxyphene treatment arm. These double-blind randomised multiple-dose studies were comparative efficacy studies ranging from 2 days to 4 weeks in duration. Two studies were included in the review of Goldstein & Turk 2005 (described above). The pain types in the studies were: back pain (2 studies), joint pain (1), osteoarthritis (3) and miscellaneous (1). Overall, analgesic efficacy of dextropropoxyphene/ paracetamol was equivalent to or less than the comparator in 6 of the 7 studies reviewed; the seventh study, which reported dextropropoxyphene/paracetamol and dextropropoxyphene as being more efficacious than paracetamol and placebo, appears to be underpowered with only 32 patients.

5.5 Unpublished clinical efficacy data

In 1972, the FDA approved two dextropropoxyphene-paracetamol products - Darvocet (dextropropoxyphene HCl and paracetamol) and Darvocet-N (dextropropoxyphene napsylate and paracetamol), on the basis of efficacy trials and a bioequivalence study.

Efficacy data submitted in 1971 included seven single-dose efficacy trials.[26] Only very limited information is available regarding these trials. These were double-blind randomised placebo controlled trials of identical design with subjects with mild to severe post-partum pain (secondary to uterine cramping or episiotomy) treated with a single dose of Darvocet (dextropropoxyphene HCl 65mg plus paracetamol 650 mg), Darvon (dextropropoxyphene HCl 65 mg), paracetamol (650 mg), or placebo. The number of patients per arm ranged from 30-48. Analgesic efficacy was assessed hourly for 6 h, total pain intensity including SPID over 6 h, and total pain relief over 6 h. Statistical analyses were limited to the first 2 h post-dose.

Six of the seven trials found dextropropoxyphene only had no statistically significant difference compared with placebo. Paracetamol showed a statistically significant difference from placebo in

[25] Bannwarth B 1999 'Risk-benefit assessment of opioids in chronic noncancer pain' Drug Safety 21(4): 283-96.
[26] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/ucm129256.pdf

all seven trials. In six of the seven trials the combination of dextropropoxyphene and paracetamol was statistically superior to placebo; one trial did not show statistical significance relative to placebo. It is unclear whether a comparison of the combination with paracetamol alone was made.

Comment

It is difficult to interpret these studies in the absence of full study details, including the baseline characteristics of the treatment groups. It is not possible to draw any meaningful conclusions from the available data regarding the comparative efficacy of the combination relative to paracetamol because no comparison appears to have been undertaken.

5.6 Summary of clinical efficacy

The available clinical data provide evidence to support the efficacy of single-dose dextropropoxyphene in combination with paracetamol for the relief of mild to moderate acute pain. Evidence from a recent meta-analysis indicates that the combination of single-dose dextropropoxyphene/paracetamol is not superior to single-dose paracetamol alone.

Dextropropoxyphene on its own did not appear to be superior to paracetamol or NSAIDs.

There are insufficient clinical data to assess the efficacy of multiple doses of dextropropoxyphene (alone or in combination) for the relief of chronic pain of any severity.

It should be noted that many of these studies were old and not performed to Good Clinical Research Practice standards. Newer methods of assessing pain relief were therefore not used. It is often difficult to prove efficacy of analgesics due to a high placebo response. There was also heterogeneity in the pain indications which may have affected the overall assessment of efficacy.

6.0 SAFETY

6.1 Published Profile

The data sheets for Capadex and Paradex state that these medicines are contraindicated with concurrent use of alcohol, concurrent use of other paracetamol containing products and known hypersensitivity to the ingredients.

The warnings and precautions for use listed in the data sheet include:

- Do not prescribe dextropropoxyphene for patients who are suicidal or addiction-prone
- Use with caution in patients taking anxiolytics or antidepressants and patients who use alcohol in excess
- Do not exceed the recommended dose and limit alcohol use

Comment

The contraindications and warnings sections are inconsistent with regard to alcohol use.

There is also information on:

- Deaths related to dextropropoxyphene
- Drug dependence
- Use in patients with hepatic or renal impairment
- Use in special populations

The section on interactions gives a brief description on use with other CNS depressants including alcohol.

The adverse effects section of the data sheet includes the following reactions:

Dizziness	Sedation
Nausea	Vomiting
Constipation	Abdominal pain
Skin rashes	Lightheadedness
Headache	Weakness
Euphoria	Dysphoria
Hallucinations	Minor visual disturbances
Liver dysfunction	Abnormal liver function tests
Reversible jaundice	Hepatic necrosis
Renal papillary necrosis	Subacute painful myopathy

The overdosage section includes information on the CNS effects, respiratory depression, cardiac problems and liver effects.

Comment

The information provided in the data sheet is consistent with that of the UK SPC at the time of withdrawal from the market in 2005.

Barkin et al 2006[1] have published a review of dextropropoxyphene. They note the following adverse effects: ataxia, dizziness, lightheadedness, cephalgia, visual disturbances, hallucinations, weakness, somnolence, drowsiness, seizures, paradoxical excitation, sleep disorders, euphoria, dependence, rashes, diaphoresis, nausea, emesis, abdominal pain, constipation, transaminase elevation, reversible jaundice, urinary hesitancy and retention. In addition the authors state that, administration to patients with hepatic or renal impairment poses a therapeutic challenge due to increased serum concentrations. The tolerance tachyphylaxis and psychological/physical dependence demonstrated with propoxyphene in their clinical practice exceeds that of codeine due to the euphoric and sense of well-being effects of propoxyphene.

Acute toxicity from propoxyphene precipitates symptoms which include: respiratory depression, circulatory collapse, pulmonary oedema, coma, seizures, nephrogenic diabetes insipidus, ECG abnormalities (intraventricular conduction disturbances, QRS prolongation, right heart block, ventricular bigeminy).

Comment

The scientific basis of some of the effects mentioned by Barkin et al is unclear, some of the mentioned effects appear to be anecdotal The paper is included here as it was referred to by Public Citizen in their petition to the FDA.

The following adverse effects noted by Barkin are not included in the data sheet: ataxia, dizziness, cephalgia, somnolence, seizures, sleep disorders, dependence, diaphoresis, urinary hesitancy and retention.

A comparison of the datasheet with the USPI for Darvon revealed the following additional ADRs in the USPI: arrhythmia, bradycardia, cardiac/respiratory arrest, congestive heart failure, tachycardia, myocardial infarction, eye swelling, drug tolerance, influenza-like illness, drug withdrawal syndrome, GI bleed, acute pancreatitis, hepatic steatosis, hepatomegaly, hepatocellular injury, hip fracture, decreased blood pressure, metabolic acidosis, ataxia, syncope, abnormal behaviour, confusional state, mental status changes, respiratory depression, dyspnoea and itch.

In addition the USPI includes stronger warnings regarding alcohol use, drug dependency, use in patients with hepatic or renal impairment, use in the elderly, use in children and use in those who are suicidal or have a history of suicidal ideation. There is also significantly more information on drug interactions and use in pregnancy and lactation.

The data sheets for Capadex and Paradex would benefit from a revision of the adverse effects section, depending on the Committee's overall risk benefit assessment of these products.

6.2. *CARM data*

Table 3. Summary of reactions reported to CARM in association with dextropropoxyphene/ paracetamol (DXP) and codeine/ paracetamol (COD)

Event Term	Number of reports		Event Term	Number of reports	
	DXP	COD		DXP	COD
Abdominal pain	5		Jaundice	1	
Aggressive reaction	1		Labyrinthine Disorder	1	
Amnesia	2		Lethargy		1
Anaphylaxis	1		Libido increased	1	
Angina Pectoris Aggravated	1		Lip swelling		1
Angioedema		2	Malaise	2	
Ataxia	3		Medication error	1	
Atrial Fibrillation	1		Mouth Ulceration	1	
Back pain	1		Nausea	6	2
Brand switch	2	10	Oedema generalised	1	
Bradycardia	1		Pallor		1
Bronchospasm (aggravated)	2	1	Palpitation	2	
Chest Pain	1		Paraesthesia	2	
Complex regional pain syndrome	1		Paroniria	1	
Confusion	3		Photophobia	1	
Conjunctivitis	1		Product formulation change	1	
Convulsions	1		Prothrombin decreased	1	
Coordination abnormal	1		Pruritis	2	2
Coughing	1		Psychosis	1	
Cramps legs	1		Rash	1	5
Creatine phosphokinase increased	1		Rash erythematous	2	
Deafness	1		Rhinitis		1
Diarrhoea		4	Rigors		1
Diplopia	1		Somnolence	4	1
Dizziness	3		Speech disorder	1	
Drug eruption	1		Suicidal tendency	1	
Drug interaction	2		Sweating increased	1	1
Dysphagia		1	Syncope	1	
Dyspnoea	1	1	Synovitis		1
Epistaxis	1	1	Tachycardia	1	
Face oedema	1		Therapeutic response decreased	4	7
Feeling of warmth	1	1	Therapeutic response increased	4	
Fever	1	1	Thrombocytopenia	1	
Flushing	1	1	Tinnitus	1	
Fracture	1		Tongue oedema	1	
Generic switch	3		Urticaria	2	2
Haemorrhage intracranial	1		Vasodilation		1
Hallucination	2		Vision abnormal	4	
Headache	1		Vision blurred		1
Hepatic enzymes increased	4		Visual disturbance	1	
Hepatic function abnormal	2		Vomiting	4	1
Hepatitis	1				
Hepatitis cholestatic	1				
Hepatocellular damage	2				
Hot flushes	1				
Hyperaesthesia	1				
Hyperventilation		1			
Hypocalcaemia	1				

CARM has received a total of 64 case reports in association with dextropropoxyphene/ paracetamol and 24 case reports in association with codeine/ paracetamol.

The higher number of reports in association with dextropropoxyphene/paracetamol may reflect the perception that codeine/paracetamol is safer as it available without prescription. It should be noted that during the medicine utilisation study for Paradex (discussed below), adverse events considered to be ADRs were added to the spontaneous report database. In addition the study may have stimulated spontaneous reporting for Paradex. Therefore the higher numbers of reports for dextropropoxyphene/ paracetamol compared to codeine/ paracetamol medicines may be in part due to stimulated reporting. The first report for Paradex was received in February 1999. By May 2007 CARM had a total of 24 reports; after Paradex was put on IMMP there were a further 14 reports.

Comment

The comparative safety of dextropropoxyphene and codeine is discussed further in section 8.

6.3 Published case reports and studies on safety

Bannwarth and Richez 2009[27] argue that co-proxamol has a strong safety record. Whilst serum alkaline phosphatase elevation is common, cholestatic or mixed hepatitis is well known, but usually asymptomatic. Hypoglycaemia is far less common and occurs chiefly in the very elderly and in patients with renal failure. A randomised double-blind trial comparing paracetamol alone, dextropropoxyphene plus paracetamol, and codeine plus paracetamol, showed that the safety profile of the Dextropropoxyphene/paracetamol combination was better than for the codeine/paracetamol cpmbination. The authors state that some patients fail to find a satisfactory alternative to dextropropoxyphene; depriving such patients may be considered unethical. In France, the number of deaths associated with co-proxamol is around 7 per year (press release from Afssaps).

Comment

The study mentioned above was discussed in section 5.4, it included 141 patients treated for one week and is therefore too small to draw any conclusions on safety.

6.3.1 Skin reactions

Machet et al 2000[28] report the case of a 43-year-old woman who was admitted for a febrile eruption of acute onset. Four days before admission she had been treated with spiramycin, tenoxicam, dextropropoxyphene, paracetamol, chlorpheniramine, caffeine and carbaspirin. Clinical examination showed generalised erythema with numerous pustules on the trunk. Histological examination of a cutaneous biopsy showed a subcorneal unilocular pustule with dermal oedema and infiltration of polymorphonuclear cells within the dermis. There was no evidence of viral infection. The patient was treated with topical corticosteroids and the lesions disappeared in 12 days. The patient had experienced two similar episodes in the last 5 years. Each episode was preceded by intake of dextropropoxyphene combined with paracetamol.

Patch testing was carried out 1 month later and was positive only for dextropropoxyphene. Therefore it was considered that the acute generalised exanthermatic pustulosis was caused by the dextropropoxyphene.

6.3.2 Hypersensitivity Reactions

Matusiewicz et al 1999[29] describes a 61-year-old man who developed hypersensitivity pneumonitis and skin rash in close association with taking co-proxamol. These problems occurred in spite of treatment with prednisolone 40mg daily (20mg daily at the time of presentation) for assumed

[27] Bannwarth B, Richez C 2009 The dextropropoxyphene controversy' Joint Bone Spine doi:10.1016/j.jbspin.2009.04.004
[28] Machet L, Martin L, Machet MC, Lorette G and Vaillant L 2000 'Acute generalised exanthematous pustulosis induced by dextropropoxyphene and confirmed by patch testing' Acta Derm Venerol 80: 224-5.
[29] Matusiewicz SP, Wallace WAH, Crompton GK 1999 'Hypersensitivity pneumonia associated with co-proxamol therapy' Postgrad Med J 75: 475-487

cranial arteritis. A therapeutic challenge with paracetamol was negative. It appeared likely that the patient's rash and hypersensitivity pneumonitis were caused by dextropropoxyphene.

Fulton and McConigal 1989[30] report a case of steroid responsive haemolytic anaemia due to dextropropoxyphene/paracetamol combination. A 71-year-old woman presented with a 6 month history of tiredness. Macrocytic anaemia was discovered; marrow examination revealed hyperactive erythropoesis, absent stainable iron and no megaloblastic features. Reticulocytes were elevated at 20% and further indirect evidence of haemolysis was provided by elevated serum bilirubin and lactic dehydrogenase. Red cell survival was reduced to 4.5 days. A trial of prednisolone 30mg/day was undertaken, and haemoglobin rose dramatically. Withdrawal of steroids as an outpatient was unsuccessful, although inpatient withdrawal was achieved. Maintenance prednisolone (10mg/day) controlled her condition for 5 years. She was readmitted some years later with significant anaemia when her history of chronic periodic and occasionally excessive intake of co-proxamol tablets was considered relevant. Her daily intake of co-proxamol varied between 4 and 8 tablets with an occasional maximum of 12 tablets. She recovered after withdrawal of co-proxamol and treatment with steroids, which were later successfully tapered and withdrawn.

6.3.3 Liver reactions

Bassendine et al 1986[31] describe three patients with recurrent jaundice, upper abdominal pain and rigors attributable to dextropropoxyphene hepatotoxicity. The diagnosis was established in each patient by rechallenge. Twelve previous patients with probable dextropropoxyphene hepatic toxicity had previously been described in the literature. Of the 15 patients, 10 had been given a diagnosis of gall stone disease. The authors noted that in the three patients described in the paper the incrimination of dextropropoxyphene was difficult and only proven by rechallenge. The authors suspect that the mechanism was immune related.

Rosenberg et al 1993[32] report nine cases of dextropropoxyphene induced hepatotoxicity. In each case the history was suggestive of large bile duct obstruction. All patients underwent ultrasound examination and percutaneous liver biopsy. The histological features of the biopsies concurred with previously reported cases of dextropropoxyphene hepatotoxicity. These features consisted of centrilobular cholestasis, portal tract inflammation and bile duct abnormalities, in all cases mimicking large bile duct obstruction. The occurrence of these 9 cases at one centre, 6 presenting within 12 months, suggests that it is much more common than previously assumed and may be misdiagnosed as large bile duct obstruction.

6.3.4 Hypoglycaemia

Lee et al[33] report the rare case of an 82-year-old woman with type 2 diabetes mellitus in end stage renal disease undergoing maintenance haemodialysis who experienced recurrent symptomatic hypoglycaemia during treatment with propoxyphene. The hypoglycaemia occurred simultaneously with elevated levels of serum reactive insulin and C-peptide. The patient recovered after stopping propoxyphene.

Shah et al[34] also report a case of propoxyphene induced hypoglycaemia. A 54-year-old man with chronic renal failure had recurrent episodes of hypoglycaemia (plasma glucose level 40 mg/dl). While he continued treatment with propoxyphene, 58 hours into a 72 hour fast the plasma glucose concentration was 38 mg/dl,and beta hydroxybutyric acid was 0.9 mmol/l with inappropriately elevated plasma insulin, serum c-peptide and proinsulin levels. A 72 hour fast after discontinuation

[30] Fulton JD and McGonigal G 1989 'Steroid responsive haemolytic anaemia due to dextropropoxyphene paracetamol combination' J Royal Soc Med 82: 228.
[31] Bassendine MF, Woodhouse KW, Bennett M and James OFW 1986 'Dextropropoxyphene induced hepatotoxicity mimicking biliary tract disease' Gut 27: 444-9.
[32] Rosenberg WMC, Ryley NG, Trowell JM, McGee J O'D and Chapman RW 1993 'Dextropeopoxyphene induced hepatotoxicity: a report of nine cases' Hepatology 19: 470-474.
[33] Lee HT, Tseng WC and Tarng DC 2007 'Recurrent hypoglycaemia in a hemodialysis patient related to propoxyphene treatment' J Chin Med Assoc; 70(7): 286-8.
[34] Shah P, Aniszweski J, Service FJ 2006 'Propoxyphene-induced hypoglycaemia in renal failure' Endocr Pract; 12(2): 170-3.

of propoxyphene therapy resulted in no hypoglycaemia and he experienced no further hypoglycaemic episodes for at least 2 years after the withdrawal of propoxyphene.

Almirall et al 1989[35] report a case of propoxyphene-induced hypoglycaemia in a patient with chronic renal failure. A 36-year-old man with ankylosing spondylitis, amyloidosis and chronic renal failure on maintenance haemodialysis developed severe hypoglycaemia while being treated with propoxyphene. On discontinuation, blood glucose levels returned to normal and hypoglycaemia did not recur. Hyperinsulinaemia was ruled out as the cause since plasma glucagons and growth hormone levels were appropriately raised and serum insulin levels adequately suppressed. The authors also note that two patients with normal renal function and propoxyphene-induced hypoglycaemia were reported in France.

6.3.5 Hip Fractures

Kamal-Bahl et al 2006[36] describe a prospective cohort study using an administrative claims data set from adults aged ≥65 years (during 1999 to 2000). The authors obtained administrative claims data concerning all active and retired employees aged 65 years or older from the 199 and 2000 MarketScan Medicare Supplemental and Coordination of Benefits data base. Each person was defined as a propoxyphene (alone) user or non-user based on propoxyphene exposure in the 14 days before each fracture event in the cohort.

A total of 362,503 patients were included in the analysis. During a mean follow-up of 464 days, around 10% (37,569) of the population had ≥1 propoxyphene prescriptions filled. One quarter of the patients were aged 65 to 69 years and 23% were aged 80 years or above. Around 1% (5065) of the cohort sustained a hip fracture. Propoxyphene users had a two-fold higher risk for hip fracture HR 2.05 (95% CI 1.87-2.29). There was a dose dependent relationship with patients taking a higher dose at higher risk of hip fracture. Other opioid analgesics were associated with an increased risk of hip fracture HR 2.28 (95% CI 2.13-2.45). Subjects using non-opioid analgesics did not have an increased risk of hip fracture HR 0.99 (95% CI 0.92-1.06) compared to non-users.

Limitations of the study given by the authors included:

- Potential misclassification as the outcome was based on diagnostic coding
- Exposure was inferred from prescription claims data
- May have been under-adjustment for potential confounders
- Residual confounding by factors that could not be measured e.g. smoking, body mass index
- The study did not assess whether the risk for hip fracture varies based on duration of propoxyphene exposure.

Comment

The most likely reason for the increase in hip fractures is that they occurred secondary to dizziness and drowsiness associated with opioid use.

6.3.6 Dependency

Zacny and Goldman 2004[37], reported the results from a small study looking at subjective effects in non-drug abusing people.

In this small study, 18 volunteers participated in a crossover, randomised, double-blind study. The volunteers were assessed to be non-drug abusers, but did have some history of drug use. The subjects received placebo, 50mg propoxyphene napsylate, 100mg propoxyphene napsylate,

[35] Almirall J, Montoliu J, Torras A and Revert L 1989 'Propoxyphene-induced hypoglycaemia in a patient with chronic renal failure' Nephron 53: 273-275.
[36] Kamal-Bahl SJ, Stuart BC and Beers MH 2006 'Propoxyphene use and risk for hip fractures in older adults' Am J Geriatric Pharmacol 4: 219-226.
[37] Zacny JP and Goldman RE 2004 'Characterising the subjective, psychomotor and physiological effects of oral propoxyphene in non drug abusing volunteers' Drug & Alcohol Dependence 73: 133-140.

200mg propoxyphene napsylate, 40mg morphine and 2mg lorazepam in six sessions with at least seven days washout between sessions. Subjects were assessed before and for 300 mins after drug administration.

Three different categories of effect were measured. Subjective effects were measured using five questionnaires/ rating scales: Addiction Research Centre Inventory, locally developed adjective rating scale, locally developed visual analogue scale, locally developed Drug Effect/Drug Liking/Take Again questionnaire and a locally developed Post Session Sequelae questionnaire. The final questionnaire was completed 24 hours after the session.

Psychomotor/ cognitive performance was measured using an eye-hand coordination test, the Digit Symbol Substitution Test, an auditory reaction test, a logical reasoning test and a locally developed recall memory test.

The physiological measures assessed were: heart rate, blood pressure, arterial oxygen saturation, respiration rate, exophoria and pupil size.

Selected mean peak or trough scores or ratings (±S.E.M.) of subjective effects for each of the six drug conditions

	PLC	50 mg PROPOX	100 mg PROPOX	200 mg PROPOX	40 mg MOR	2 mg LZP
ARCI						
PCAG[a,b]	6.6 (0.9)	6.6 (0.7)	6.1 (0.7)	8.0 (0.6)	10.0 (0.7)*	11.0 (0.7)*
AMP	3.4 (0.7)	3.6 (0.7)	3.3 (0.7)	4.3 (0.7)	4.8 (0.6)*	4.0 (0.6)
LSD[a,b]	4.4 (0.3)	3.8 (0.4)	3.5 (0.2)	4.2 (0.4)	6.9 (0.6)*	6.3 (0.6)*
Adjective rating scale						
Dry mouth[a]	0.6 (0.2)	0.4 (0.2)	0.7 (0.3)	0.6 (0.2)	1.2 (0.3)	1.1 (0.2)
Flushing[a]	0.2 (0.1)	0.1 (0.1)	0.0 (0.0)	0.2 (0.1)	0.7 (0.2)*	0.2 (0.1)
Numb[a]	0.1 (0.1)	0.0 (0.0)	0.1 (0.1)	0.2 (0.2)	0.7 (0.2)*	0.5 (0.1)
Skin itchy[a]	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2 (0.2)	0.9 (0.3)*	0.2 (0.1)
Vomiting	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.9 (0.4)*	0.2 (0.2)
VAS						
Difficulty concentrating[a,b]	18.9 (6.1)	16.9 (6.3)	16.9 (5.5)	22.1 (6.3)	33.1 (8.5)	57.1 (8.4)*
Dizzy[a,b]	6.1 (3.5)	5.7 (2.2)	5.7 (3.1)	7.4 (3.4)	23.7 (7.7)	40.2 (8.6)*
Feel bad[a,b]	8.7 (2.8)	9.7 (4.2)	10.2 (4.6)	11.6 (4.1)	21.6 (6.9)	33.6 (8.6)*
Having unpleasant						
bodily sensations[a]	9.1 (3.4)	11.9 (6.3)	2.7 (1.0)	10.9 (4.9)	27.8 (8.1)	22.6 (8.2)
Heavy or sluggish feeling[a,b]	22.4 (5.9)	23.2 (6.5)	14.6 (4.7)	36.8 (7.2)	54.9 (7.2)*	51.6 (7.7)*
High[a,b]	6.8 (3.4)	3.9 (1.5)	2.7 (1.0)	5.3 (1.8)	24.3 (8.1)	37.3 (8.9)*
Hungry[a,b,c]	33.2 (7.7)	34.7 (8.2)	34.4 (8.2)	36.8 (9.0)	32.1 (8.8)	33.2 (8.2)
Nauseous	4.9 (1.8)	9.5 (5.6)	4.2 (1.8)	6.9 (2.0)	29.3 (9.7)*	24.9 (8.7)
Sleepy[a,b]	39.1 (7.3)	39.2 (6.0)	39.8 (5.5)	52.4 (7.7)	62.1 (7.6)*	64.7 (7.0)*
Tingling[a]	4.2 (1.8)	3.6 (1.4)	9.2 (5.8)	6.2 (3.3)	26.7 (6.4)*	12.3 (4.2)
Drug Effect/Drug Liking/Take Again						
Feel drug[a,b]	1.9 (0.3)	2.1 (0.2)	2.2 (0.2)	2.7 (0.2)	3.8 (0.2)*	3.3 (0.3)*
Like drug[a]	44.9 (3.0)	43.6 (1.8)	44.3 (1.5)	38.3 (3.2)	28.3 (4.6)*	35.0 (4.0)

PLC, placebo; PROPOX, propoxyphene; MOR, morphine; LZP, lorazepam. Results from time course analyses are also included in this table.

[a] Time course analysis: significant drug effect or drug × time interaction, post hoc testing determined 40 MOR significantly different from placebo.

[b] Time course analysis: significant drug effect or drug × time interaction, post hoc testing determined 2 LZP significantly different from placebo.

[c] Trough rating.

* $P < 0.05$ compared with placebo.

Morphine and lorazepam produced subjective effects (see table above) as measured by the questionnaires described above. There were no statistically significant subjective effects obtained with any dose of propoxyphene in the group as a whole, but 30-50% of the subjects did appear to experience adverse effects on psychomotor or cognitive performance. Both propoxyphene and morphine produced meiosis.

Dore 1996[38] reports a case that highlights the potential for abuse of dextropropoxyphene. The author reports a female who was addicted to dextropropoxyphene as an alternative to other opioids. She was treated with methadone and psychosocial interventions with improved physical health and functioning.

[38] Dore GM 1996 'The dangers of dextropropoxyphene' Aust NZ J Psychiatry; 30: 864-6.

Ramsay 1991[39] reported a case of complete nerve deafness after abuse of co-proxamol. A 44-year old woman was admitted to hospital with a 4 month history of increasing deafness and weight loss (30kg on admission). Over the previous 4 years she had noticed intermittent episodes of deafness. Pyoderma gangrenosum had developed 8 years earlier with no underlying cause found. Audiological tests confirmed severe bilateral sensorineural deafness. It was disclosed that the patient had been prescribed co-proxamol 20 years earlier and had continued to take it. She obtained the drug by persistently asking for a prescription from her general practitioner, by using a friend's prescription and by taking tablets from work. Normally she took about 4 tablets a day but had increased to 30 tablets a day concurrent with the increasing deafness, due to pain from her pyoderma. The authors note 2 previous reports of deafness associated with overdose of co-proxamol and spontaneous reports to the UK regulator of transient deafness and tinnitus in patients taking therapeutic doses.

Ng and Alvear 1993[40] investigated the profile of dextropropoxyphene abusers in the detoxification unit in the Mental Heath Institute in Mexicali, Mexico. A total of 209 records were reviewed,:73 were included in the study. Most of the subjects were single unemployed males with a history of at least 4 years continuous dextropropoxyphene abuse. They were consuming an average dose per day 3.5 times higher than the maximum recommended dose. The onset of generalised seizures associated with dextropropoxyphene abuse was confirmed in 56.3% of cases.

Dextropropoxyphene was the first opiate ever abused in 67% of the cases. This suggests that dextropropoxyphene is an opiate of primary abuse.

6.4 Summary of safety in therapeutic use

The data discussed above shows that the current data sheets do not accurately reflect the safety profile of dextropropoxyphene/paracetamol products. Additional side effects which should be described in the data sheets include: hypoglycaemia, hip fracture, ataxia, syncope and abnormal behaviour. More information could be included on hypersensitivity reactions.

The warnings and precautions should include additional information on drug interactions, dependency, hepatic effects, use in those with suicidal tendencies, and use in special populations.

There did not appear to be any published evidence of cardiotoxicity at therapeutic dose of these medicines, although the pre-clinical studies described below suggest that there may be unrecognised cardiac effects.

7.0 OVERDOSE

7.1 New Zealand Poisons Centre Data

The New Zealand Poisons Centre has provided summary information on cases of death and hospitalisation associated with dextropropoxyphene and codeine (see Tables 4 & 5).

Table 4: Deaths due to dextropropoxyphene compared with codeine

Year	Dextropropoxyphene*		Codeine	
	Primary substance	Contributing substance	Primary substance	Contributing substance
2004	4	5	2	5
2005	2	2	6	4
2006	2	4	3	6
2007	1	0	5	2

* The data has been reanalysed and is slightly different from that previously reported. The data for 2001-2002 is discussed below.

[39] Ramsay BC 1991 'Complete nerve deafness after abuse of co-proxamol' Lancet; 338: 446-7

[40] Ng B and Alvear M 1993 'Dextropropoxyphene addiction – a drug of primary abuse' Am J Drug Alcohol Abuse 19: 153-8.

Table 5. Hospitalisations due to dextropropoxyphene compared with codeine

Year	Dextropropoxyphene*		Codeine#	
	Primary diagnosis (age range)	Secondary diagnosis (age range)	Primary diagnosis	Secondary diagnosis
2004	12 (3-79)	22 (15-79)	41	71
2005	12 (16-70)	17 (16-66)	51	76
2006	9 (19-97)	22 (3-97)	67	157
2007	23 (1-87)	24 (14-78)	118	92
2008	N/A	N/A	185	88

* The data has been reanalysed and is slightly different from that previously reported.

Not including dihydrocodeine, pholcodine or Codral

There appears to have been a reduction in deaths due to dextropropoxyphene since 2001-2002. The number of deaths and hospitalisations due to dextropropoxyphene is lower than for codeine.

Comment

It should be noted that the rates of reporting are likely to be lower than the actual number of cases as previous studies in the UK have shown (see below).

The greater number of hospitalisations due to codeine ingestion may reflect the availability of codeine without a prescription. The status of codeine-containing products is under review.

It should be noted that some of the hospitalisations due to dextropropoxyphene ingestion occurred in children, most likely due to exploratory behaviour. This reflects the published data[47] showing that not all deaths due to dextropropoxyphene occur in patients for which the medicine is prescribed

The New Zealand data reflects the greater lethality of dextropropoxyphene compared with codeine (also discussed further below); since the ratio of deaths to hospitalisations is higher for dextropropoxyphene than for codeine.

7.2 Case Studies

The lethal effects of dextropropoxyphene in overdose are caused in general by respiratory depression (as for all opiates) and cardiotoxicity (see data sheets).

Whitcomb et al 1989[41] report a case of propoxyphene overdose in which marked QRS widening (100msec on admission) was reversed by lidocaine. The patient had taken a massive propoxyphene overdose and had profound central nervous system and cardiac toxicity with convulsions, respiratory depression, bradycardia, marked QRS widening and hypotension. The bradycardia was reversed by adrenaline. The authors noted that lidocaine administration repeatedly narrowed the widened QRS complex. Lidocaine treatment had a beneficial effect and the patient survived.

Ruane et al 1989[42] report a case of overdose of 120 co-proxamol tablets where the patient survived. The patient was a 19-year-old man who was admitted to hospital having been found unconscious and fitting at home. On admission he was deeply cyanosed, unconscious, apnoeic and convulsing. His pupils were dilated, blood pressure was unrecordable, cardiac rhythm was sinus bradycardia, and blood sugar was 4.2mmol/l. He was treated with ventilation, diazepam, paraldehyde, naloxone, doxapram and n-acetylcysteine.

[41] Whitcomb DC, Gilliam FR III, Starmer F and Grant AO 1989 'Marked QRS Complex abnormalities and sodium channel blockade by propoxyphene revered with lidocaine. J Clin Invest 84: 1629-1636.
[42] Ruane BJ, Glover G and Varma MPS 1989 'Survival after an overdose of distalgesic (dextropropoxyphene and paracetamol). Ulster Med J 58: 187-9.

7.3 Published literature

Ulens et al 1999[43] report the results of *in vitro* studies measuring the effects of norpropoxyphene (the major metabolite of dextropropoxyphene) on cardiac ion channels in xenopus oocytes expressing human HERG channels. Low drug concentrations (5 µmol/l) facilitated HERG currents. Higher drug concentrations blocked HERG currents: IC_{50} approx 40 µmol/l. There was a dramatic shift in the reversal potential to a more positive value due to a 30 fold increased sodium ion permeability. The authors note that toxic blood concentrations of 3 to180 µmol/l have been reported. The cardiotoxic effects of norpropoxyphene cannot be reversed by naloxone.

Comment

The therapeutic concentration of dextropropoxyphene is around 0.1-0.4 µmol/l, the volume of distribution indicates that the concentration of dextropropoxyphene in the tissues is likely to be higher. Therefore an effect on the heart at therapeutic doses cannot be ruled out.

Afshari et al 2005[44] investigated ECG changes following dextropropoxyphene overdose. A prospective study was conducted on 15 patients and controls with overdose. A retrospective study of a cohort of 159 dextropropoxyphene overdoses from Edinburgh and Newcastle Australia was also conducted. The four hour paracetamol concentration was used as a surrogate for the amount of dextropropoxyphene ingested. Dextropropoxyphene overdose resulted in a statistically significant QRS prolongation mean: 99.36 (95% CI 96.19-102.53) msec. QRS with other combination opioid-paracetamol products was 82.84 (95% CI 80.81-84.88) msec. In the retrospective study a dose dependent effect was documented, although the correlation coefficient relating paracetamol level to effect was relatively weak (r=0.338; p=0.003; n=74).

Simkin et al 2005[45] reviewed the international literature related to cases of self poisoning with co-proxamol. They noted that in England and Wales between 1997-1999, 18% of drug-related suicides involved co-proxamol; these constituted 5% of all suicides. Death usually resulted from the toxic effects of dextropropoxyphene on respiration or cardiac function. Death may occur rapidly and the lethal dose can be relatively low. The majority of deaths occurred before hospital treatment could be received. The authors also noted that the risk can extend to others in the household of the person for whom the drug is prescribed.

The first death associated with dextropropoxyphene was reported in 1964 and concerns about its increasing use for self poisoning were raised in the 1970s both in the UK and USA. An overdose of as few as 15 to 20 tablets can be fatal, especially if taken in conjunction with alcohol or another CNS depressant. The paracetamol component of co-proxamol rarely contributes directly to death.

In the 1970's in the USA, propoxyphene was noted to cause between 1000 and 2000 deaths per year. In 1978 and 1980 the FDA carried out an informational campaign to try and reduce inappropriate prescribing. Analysis by Soumerai et al[53] of deaths between 1977 and 1980 indicated that the risk of propoxyphene-related death remained constant at 52 deaths per million prescriptions (discussed more fully in section 9).

Simkin et al[45] noted that in an Australian study of deaths between 1989 and 1992, analgesics containing dextropropoxyphene had the fourth highest risk of self-poisoning mortality when adjusted for prescription numbers. Dextropropoxyphene was the most common single drug cause of death in the study, although it was noted that the number of dextropropoxyphene deaths had decreased since earlier studies.

Several studies conducted in Scandinavian countries showed a similar high number of deaths associated with dextropropoxyphene.

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[43] Ulens C, Daens P and Tytgat J 1999 'Norpropoxyphene-induced cardiotoxicity is associated with changes in ion-selectivity and gating of HERG currents' Cardiovascular Research 44: 568-78.
[44] Afshari R, Maxwell S, Dawson A and Bateman DN 2005 'ECG abnormalities in co-proxamol poisoning' Clinical Toxicol 43: 255-9.
[45] Simkin S, Hawton K, Sutton L, Gunnell D, Bennewith O and Kapur N 2005 'Co-proxamol and suicide: preventing the continuing toll of overdose deaths' Q J Med 98: 159-170.

In the UK, it was calculated from a study of coroners' files between 1976 and 1980 that the national mortality data under-estimated deaths from the dextropropoxyphene/paracetamol combination by 39%. In the UK, prescription numbers for dextropropoxyphene reached a peak around 1978 and declined subsequently. The number of deaths followed the prescription numbers. An overall mortality rate of 10.6% for co-proxamol overdoses was calculated compared with 2.3% for analgesics as a whole. Between 1999 and 2002 there were 2.9 suicide deaths per 100,000 prescriptions for co-proxamol in England and Wales. Comparable figures for antidepressants were 5.3 deaths/100,000 prescriptions for tricyclic antidepressants and 0.4 for SSRIs.

High levels of alcohol in toxicology reports have been recorded in several studies. It has been estimated that alcohol contributed to death in 757 (52%) of dextropropoxyphene suicides in England. Studies where the information was available have recorded deaths resulting from as few as 10 tablets. Only 11% of the fatal dextropropoxyphene overdoses in England received hospital treatment.

Hawton et al 2003[46] reported the outcome of a study of national mortality statistics and local non-fatal self- poisonings with co-proxamol in England and Wales during the period 1997-1999. Of 4162 drug related suicides, 766 (18%) involved co-proxamol alone, 368 (9%) involved paracetamol alone. The odds of dying after overdose with co-proxamol were 2.3 times (95% CI 2.1-2.5) those for tricyclic antidepressants and 28.1 (24.9-32.9) times those for paracetamol.

Table 6: Comparison of numbers (95% confidence intervals) of drug related suicides and undetermined deaths in England and Wales with non-fatal self- poisoning in Oxford 1997-1999 for co-proxamol, paracetamol and tricyclic antidepressants (used alone)

	Co-proxamol	Tricyclic antidepressants	Paracetamol
Deaths in England and Wales/year	255 (238-274)	309 (289-330)	123 (110-136)
Non-fatal self poisonings in Oxford/year	26 (21-33)	73 (64-83)	356 (335-378)
Odds ratio for relative lethality compared with paracetamol	28.1 (24.9-32.9)	12.3 (11.5-13.2)	1.0
Odds ratio for relative lethality compared with tricyclic antidepressants	2.3 (2.1-25)	1.0	0.08 (0.08-0.09)

Hawton et al 2004[47] reported the outcome of a multi-centre study of co-proxamol poisoning suicides in England between January 2000 and December 2001. The authors identified 123 co-proxamol poisoning suicides. Alcohol was involved in 58.5% of the overdoses; these individuals generally had lower blood drug levels and consumed fewer tablets. Younger people were more likely to have consumed alcohol and have lower levels of suicide intent. Nearly half the individuals had a history of self harm and a third were under psychiatric care. Co-proxamol had been prescribed for the individual in 81.5% of cases. In other cases, the source of the co-proxamol was nearly always a family member or partner. The largest proportion of deaths occurred in people aged 55 years and over; this reflects prescribing patterns. Suicidal intent generally tends to be higher in older than younger people who take overdoses. Older people are generally more vulnerable to the toxic effects of co-proxamol.

Jonasson et al 1999[48] analysed the involvement of dextropropoxyphene in fatal poisonings in Sweden. The authors noted that the frequency of fatal poisoning was constantly high. 834 cases of dextropropoxyphene-related death over a 5 year period (1992-1996) were reviewed. The ratio between the number of fatal poisonings and the prescription rate (defined as defined daily dose/1000 inhabitants during a 12 month period) was determined. The highest ratio of 27 was

[46] Hawton K, Simkin S, Deeks J 2003 'Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings' BMJ 326: 1006-8.
[47] Hawton K, Simkin S, Gunnell D, Sutton L, Bennewith O, Turnbull P and Kapur N 2004 'A multicentre study of co-proxamol poisoning suicides based on coroner's records in England' B J Clin Pharmacol 59: 207-212.
[48] Jonasson U, jonasson B and Saldeen T 1999 'Correlation between prescription of various dextropropoxyphene preparatiosn and their involvement in fatal poisonings' Foresnsic Sci Int. 103: 125-132.

attributed to dextropropoxyphene alone, the ratio for the combination with paracetamol was 6.3. The dextropropoxyphene-only preparations represented 26% of all dextropropoxyphene prescriptions, but were implicated in 62% of the dextropropoxyphene deaths.

Distribution of fatal poisonings ascribed to DXP alone, DXP+paracetamol, DXP+phenazone and DXP+chlorzoxazone during the years 1992–1996, the prescription rate in DDD and fatal poisoning/DDD, and mean quotients of each preparation during the 5-year period

Year	Fatal poisoning total	DXP alone			DXP+paracetamol			DXP+phenazone			DXP+chlorzoxazone		
		Fatal poisoning	Prescription		Fatal poisoning	Prescription		Fatal poisoning	Prescription		Fatal poisoning	Prescription	
		n	DDD	*n*/DDD	*n*	DDD	*n*/DDD	*n*	DDD	*n*/DDD	*n*	DDD	*n*/DDD
1992	132	80	3.2	25	38	8.8	4.3	10	1.4	7.1	4	1.7	2.3
1993	177	92	3.3	27.8	72	8.5	8.5	10	1.4	7.1	3	1.5	2.3
1994	155	91	3.8	24	56	8.4	6.6	4	1.0	4.0	4	1.4	2.9
1995	170	118	4.2	28	44	8.5	5	6	0.9	6.7	3	1.3	1.5
1996	200	136	4.6	29.5	57	8.0	7	5	0.7	7.1	2	1.3	1.5
	834	517	3.8	27	267	8.4	6.3	35	1.1	6.4	15	1.4	2.0

Jonasson et al 1999[49] reported that suicides may be over-reported and accidents under-reported among fatalities due to dextropropoxyphene. The authors retrospectively analysed the process leading to the classification of manner of death in cases of fatalities associated with dextropropoxyphene. Of 4306 autopsy cases, dextropropoxyphene fatality was found in 113 (2.6%). Suicide was recorded in 84 (74%) of these cases and an undetermined manner of death in 24 (21%).

Explicit unambiguous expressions of the intent of the decedent were found in 29 (26%) of 109 analysed cases (4 cases could not be analysed). In 46 cases only implicit data were found. It was concluded that the classification of the manner of death was often based on very limited grounds. Considerable under-reporting of accidents and probably over-reporting of suicides were found.

Comment

It is difficult to know whether the situation in New Zealand is similar to that in Europe, although the Poisons Centre data and the published papers discussed below indicate that dextropropoxyphene has been associated with deaths, it is not clear that the magnitude of the problem is the same.

Reith et al 2005[50] analysed opioid poisoning deaths in New Zealand between 2001 and 2002. There were 92 poisoning deaths involving opioids, of which 16 were due to dextropropoxyphene (12 were due to codeine/dihydrocodeine). The rate of deaths per 100,000 prescriptions was 2.5 (95% CI 1.45 to 4.12) for dextropropoxyphene (the rate for methadone was 0.40 (0.27-0.56)). The rate could not be estimated for codeine containing preparations as these are available over the counter. As the authors state, opioids are commonly used in the treatment of the terminally ill, patients with comorbidities and substance abusers; all of these patients have a greater mortality risk than the general population.

[49] Jonasson B, Jonasson U and Saldeen T 1999 'Suicides may be overreported and accidents underreported among fatalities due to dextropropoxyphene J Forensic Sci Int 44: 334-8.
[50] Reith D, Fountain J and Tilyard M 2005 'Opioid poisoning deaths in New Zealand (2001-2002) NZJM 118: U293

Table 7: New Zealand poisoning deaths due to opiates 2001-2002

Substance	Prescriptions	Primary cause deaths	Rate /100000 prescriptions (95% CI)	Total related deaths	Rate/100000 prescriptions (95%CI)
DXP/ DXP-P	630,655	8	1.27 (0.55-2.50)	16	2.5 (1.45-4.12)
Morphine*	555,371	30	5.40 (3.65-7.71)	33	5.94 (4.09-8.34)
Methadone	2,308,646	30	1.30 (0.87-1.86)	31	1.34 (0.91-1.91)
Substance	**DDDs**	**Primary cause deaths**	**Rate/ 100000 DDDs (95% CI)**	**Total Related Deaths**	**Rate/ 100000 DDDs (95% CI)**
DXP/ DXP-P	11,682,679	8	0.07 (0.03-0.14)	16	0.14 (0.08-0.22)
Morphine*	3,508,069	30	0.86 (0.58-1.22)	33	0.94 (0.65-1.32)
Methadone	7,830,402	30	0.38 (0.26-0.55)	31	0.40 (0.27-0.56)

* includes heroin

DXP = dextropropoxyphene; DDD = defined daily doses (200mg for DXP HCl, 300mg for DXP napsylate, 100mg for morphine and 25 mg for methadone); CI = confidence interval

Comment

Whilst opioids are used to treat patients at higher risk of death than the general population, the treated population is not the same for all opioids. Since dextropropoxyphene is regarded as a weak opioid used for mild to moderate pain, presumably these patients are not at the same risk of death as those taking morphine for severe pain or those taking methadone for substance abuse. Similarly the rates for morphine may be an overestimate as heroin deaths were included.

Dukes et al 1992[51] investigated the causes of death in intravenous drug users attending a clinic in Wellington between 1972 and 1989. 997 patients were registered for treatment; there were 67 reported deaths. Deaths were due to trauma (7), suicide (8) and accident (28). There were 28 drug-related deaths (23 accidental, 5 suicides) reported to be due to dextropropoxyphene (6), methadone (4), heroin (2), morphine (2), other opiates (4), barbiturates (6) and choral hydrate (2). In this study 26% of accidental overdoses were due to dextropropoxyphene. The authors note that a study of Wellington coronial autopsies following deaths from drugs found dextropropoxyphene to be the most common opioid drug causing death.

7.4 Summary of information on overdose

The evidence discussed above points to dextropropoxyphene being dangerous in overdose, more so than other analgesics used for mild to moderate pain. Dextropropoxyphene and its metabolite nordextropropoxyphene cause respiratory depression and cardiotoxicity- specifically QT prolongation which can result in sudden death. The actual lethal dose cannot be calculated as it varies with the individual, possibly due to differences in metabolism or polymorphisms in HERG channels. There appears to be a tolerance effect which may change the response in an individual over time. The lethal dose is also affected by alcohol intake and concomitant use of other medicines. In addition the elderly may be more susceptible.

It has also been noted that many of the people who died did so before they reached hospital, some within one hour of taking the overdose. Whilst the opiate effects of dextropropoxyphene on respiration can be reversed by naloxone, the cardiac effects cannot.

Not all of the fatal and non-fatal overdoses appear to have been intentional. This may highlight a difficulty in taking the medicine safely, perhaps due to the interactions with alcohol and other medicines.

The dangers of dextropropoxyphene are not confined to those for whom the drug is prescribed. The data on hospitalisation in New Zealand also reflect this as several children are noted to have been hospitalised after dextropropoxyphene exposure.

[51] Dukes PD, Robinson GM and Robinson BJ 1992 'Mortality of intravenous drug users: attenders of the Wellington Drug Clinic 1972-89' Drug and Alcohol Review; 11: 197-201

The information above highlights the dangers of prescribing dextropropoxyphene-containing medicines to patients with high alcohol consumption or a history of self harm, or to those under psychiatric care or taking concomitant medicines that interact with dextropropoxyphene.

The FDA review of overdose information from the US concluded that there was no good evidence of marked cardiotoxicity in overdose as a cause of death.

The published papers indicate that there was a significant problem with dextropropoxyphene overdose cases, but it is not clear that this is still the case.

The Committee may consider that the current data sheets do not contain sufficient warnings in this respect.

8.0 COMPARISON WITH ALTERNATIVE ANALGESICS

Tavassoli et al 2009[52] compared the reporting rate of adverse reactions to the French pharmacovigilance system for dextropropoxyphene, tramadol and codeine (in combination with paracetamol).

Table 7: Frequency of ADRs registered in the French Pharmacovigilance Database with dextropropoxyphene, tramadol and codeine in combination with paracetamol between 1 Jan 1987 and 31 December 2006.

Parameters	DXP + P No. of case reports	Frequency per 10^5 pt-years	TRM + P No. of case reports	Frequency per 10^5 pt-years	COD + P No. of case reports	Frequency per 10^5 pt-years
Number of ADRs	3553	24.9	292	44.5	573	12.5
Number of Serious ADRs	1357	9.5	96	14.6	165	3.6
Death due to ADRs	42	0.3	1	0.2	6	0.1
Gastrointestinal ADRs	557	3.9	106	16.2	120	2.6
Cardiac ADRs	56	0.4	6	0.9	14	0.3
Vascular ADRs	83	0.6	16	2.4	19	0.4
Neurological ADRs	385	2.7	65	9.9	80	1.7
Seizure	23	0.2	7	1.1	2	0.0
Peripheral neuropathy	16	0.1	0	0.0	1	0.0
Abnormal movements	33	0.2	18	2.7	15	0.3
Cephalagia	106	0.7	6	0.9	19	0.4
Psychiatric ADRs	222	1.6	35	5.3	53	1.2
Delirium and confusion	106	0.7	19	2.9	12	0.3
Behavioural disorders	58	0.4	15	2.3	5	0.1
Hepatobiliary ADRs	967	6.8	17	2.6	79	1.7
Cutaneous ADRs	852	6.0	61	9.3	183	4.0
Metabolic Disorders	189	1.3	12	1.8	6	0.1
hypoglycaemia	118	0.8	4	0.6	0	0.0

The French pharmacovigilance system was first established in 1973 and consists of a network of 31 regional centres. The French Pharmacovigilance Database was established in 1985 to record spontaneous reporting of ADRs. Reporting of serious or unlabelled ADRs to the French Regional Centres has been mandatory for any drug prescriber since 1995. Serious reports submitted from 1 January 1987 to 31 December 2006 for dextropropoxyphene/ paracetamol (DXP+P), tramadol/ paracetamol (TRM+P) or codeine/ paracetamol (COD+P) were analysed. Usage data was also obtained and consumption was expressed in person years using the defined daily dose according to WHO.

[52] Tavassoli N, Lapeyre-Mestre M, Sommet A, Montastruc J-L and the French Association of Regional Pharmacovigilance Centres 2009. 'Reporting rate of adverse drug reactions to the French Pharmacovigilance system with three step 2 analgesic drugs: dextropropoxyphene, tramadol and codeine (in combination with paracetamol) Br J Clin Pharmacol 68: 422-6

Usage was:

- 14,247,943 person years for DXP+P from 1 January 1987 to 31 December 2006.
- 655,746 person years for TRM+P from 1 January 2003 to 31 December 2006.
- 4,575,058 person years for COD+P from 1 Jan 1987 to 31 December 2006.

Comparison of DXP+P and COD+P showed that the rate and seriousness of reported ADRs were significantly higher with the DXP+P. The rate of deaths was more marked, but not significantly so, with DXP+P. Gastrointestinal, neurological, hepatobiliary, cutaneous and metabolic ADRs were significantly more frequent with DXP+P.

Study limitations as defined by the authors were:

- Under-reporting (reporting rate in France estimated to be 5-10%),
- More recent launch of tramadol with likely higher reporting rate
- Possible difference in target population due to differences in time periods for analysis.

Comment

Dextropropoxyphene appears to associated with a higher rate of reporting of ADRs than codeine. The review of the French data appears to reflect the distribution of data in the CARM database.

Table 9: Most commonly associated adverse events of analgesic alternatives to propoxyphene as defined by the FDA

Alternative	Common Adverse Events
Aspirin	Gastrointestinal bleeding, tinnitus, hypersensitivity, asthma
Paracetamol	Hepatotoxicity
NSAIDs	Gastrointestinal bleeding, serious cardiovascular events, renal injury, liver injury, serious skin reactions
Tramadol	Respiratory depression, seizures, nausea, vomiting, serotonin syndrome
Hydrocodone/ paracetamol	Nausea, vomiting, constipation, addiction, hepatotoxicity
Codeine/ paracetamol	Constipation, sedation, nausea, vomiting
Stronger opioids	Respiratory depression, apnoea, nausea, vomiting, constipation, addiction

The FDA was particularly concerned that the adverse event profiles for alternative drugs were less favourable (see above for an overview).

9.0 EFFECT OF DEXTROPROPOXYPHENE RESTRICTIONS AND WITHDRAWAL

Soumerai et al 1987[53] reported an analysis of the effect of government and commercial warnings on reducing prescription misuse of propoxyphene. The campaign included mailed warnings, face to face education of prescribers, press releases and labelling changes. It should be noted that the mailed and person to person elements of the educational campaign were conducted by the manufacturers of propoxyphene products. The goals included a reduction in propoxyphene use with alcohol or other CNS depressants, reduced prescribing of refills, and cessation of prescribing for patients at risk of abuse and misuse (suicide).

An audit of the person to person communication by the FDA concluded that the manufacturers had not met their commitment for a personal contact informational campaign intended solely to sensitise prescribers and dentists to the precautions necessary for safe use of propoxyphene products. Over 75% of detailers left free samples of propoxyphene product at the person-to-person meeting.

[53] Soumerai SB, Avorn J, Gortmaker S and Hawley S 1987 'Effect of government and commercial warnings on reducing prescription misuse: The case of propoxyphene' AJPH 77: 1518-1532.

The FDA recommended that all physicians write 'no refill' on propoxyphene prescriptions and that all prescriptions should be ordered in writing, not by phone. This recommendation was essentially a request that physicians voluntarily behave as if the drug had been rescheduled to a higher category of the US Controlled Substances Act. This recommendation was publicly criticised by the manufacturer.

During the period in which the warnings were being issued, propoxyphene use nationwide continued a pre-existing decline of about 8% per year, but this decline halted after the warnings ceased. The 'no refill' recommendation had no impact on refill rates. There were no changes in the age and sex distributions of propoxyphene recipients. The risk of overdose death per propoxyphene prescription filled remained constant from 1979 at around 52 deaths per million prescriptions dispensed, a total of around 1100 deaths per year. In 1983, the number of propoxyphene-related deaths reported to the US monitoring system was 261, only slightly lower than for cocaine-related deaths (314). In conclusion, the data suggest that the educational campaign failed.

The authors state the limitations of the study to be:

- Aggregate data can not address such difficult-to-measure outcomes as reduced prescribing for suicidal or depressive patients
- Stabilisation in use may reflect a hard core of patients who were addicted or demanded the drug be prescribed
- There may have been a substitution effect of NSAIDs to explain the early decline in propoxyphene use.

Simkin et al 2005[45] reviewed the effect of governmental actions to restrict the use of dextropropoxyphene-containing medicines in Denmark. In 1982 the Danish National Board of Health (DNBH) wrote to all physicians warning them not to prescribe dextropropoxyphene to known alcohol or drug addicts. Failure to comply would result in disciplinary action. This action did not appear to have any effect. There was, however, a fall in deaths following a publicity campaign by the DNBH and publication of several papers in the Danish Medical Journal. The most effective measure appeared to be requiring all prescriptions for dextropropoxyphene to be registered centrally to facilitate the tracing of physicians who did not comply with guidelines.

Gaubert et al 2009[54] report on the impact on analgesic drug consumption of withdrawal of dextropropoxyphene from a French university hospital. In 2005 dextropropoxyphene was withdrawn from the formulary of Toulouse University hospital due to concerns regarding its lack of efficacy, risk of serious adverse drug reactions, possible lethality after overdose, risk of accumulation in elderly patients or those with renal failure, pharmacokinetic differences due to genetic polymorphisms and different half lives for dextropropoxyphene and paracetamol. The study compares the use of analgesics before (2003) and after (2006) dextropropoxyphene withdrawal. Drug consumption was expressed in defined daily doses for 1000 hospitalisation days. The DDD for dextropropoxyphene was considered to be 120mg.

Before the withdrawal, dextropropoxyphene was the second most used analgesic drug after paracetamol alone. After withdrawal, total consumption of analgesic drugs decreased by 4.6% (2006 compared to 2004). There was a 28% decrease in consumption of step 2 analgesics, with an increase in tramadol and decrease in codeine. Step1 analgesic consumption increased by 11% (mainly paracetamol); step 3 analgesic use decreased. The results show that dextropropoxyphene withdrawal was not associated with a marked switch in prescriptions towards other analgesic drugs. The authors believe that the results may indicate a misuse of dextropropoxyphene. They suggest that there may be over-consumption linked to abuse in some inpatients. Further investigation revealed that the decrease in step 2 analgesic consumption was particularly significant in psychiatry wards. Another explanation is that the over-consumption could be due to

[54] Gaubert S, Vie M, Damane-Michel C, Pathak A and Montastruc J-L 2009 'Dextropropoxyphene withdrawal from a French university hospital: impact on analgesic drug consumption' Fundamental and Clinical Pharmacology 23: 247-252.

personal use among medical staff as self-medication. The authors state that their findings underline that better pain management does not necessarily involve higher analgesic drug consumption.

Table 10: Analgesic Drug consumption from 2000 to 2006 (in DDD/1000D) in Toulouse University Hospital

Analgesic	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
Oral and rectal paracetamol	235.45	224.91	265.63	266.88	285.48	318.73	321.14
Total step 1	379.53	359.67	392.75	402.25	424.55	464.55	469.37
Dextropropoxyphene+ paracetamol	171.15	159.37	185.16	155.42	139.02	45.84	0
Codeine	0.37	0.35	0.4	0.53	0.57	0.51	0.58
Codeine + paracetamol	66.8	62.59	61.09	49.22	41.56	47.03	39.58
Tramadol	14.18	20.31	29.04	30.61	29.28	42.24	43.78
Tramadol + paracetamol	0	0	0	0	5.15	25.91	47.04
Injectable tramadol	1.3	2.26	3.28	5.74	8.01	10.6	13.55
Total step 2	275.12	275.48	316.22	273.54	264.58	216.94	190.31
Total step 3	50.99	50.02	60.28	57.12	65.96	65.52	61.21
Total Use	**705.64**	**685.17**	**769.25**	**732.91**	**755.09**	**747.01**	**720.89**

The weaknesses of the study as identified by the authors included:

- The DDD for dextropropoxyphene may have been too low; however reanalysis using 180mg as the DDD did not change the results
- Only drug delivery and not consumption was measured
- Patients could have been switched to NSAIDs (data not shown in this study report); however the authors state that they found no significant change in consumption of NSAIDs between 2004 and 2006
- There may have been changes in patient characteristics during the time course of the study. The authors state, however that there were no changes in bed number allocations between different specialties during the course of the study.

Ottewell and Walker wrote to Rheumatology in 2008[55] regarding the withdrawal of co-proxamol in the UK. The authors performed an audit to determine whether patients had managed to successfully transfer to an alternative painkiller. The department database (Musculoskeletal Unit, Freeman Hospital, Newcastle-upon-Tyne, UK) was searched for all patients who were current users of co-proxamol in January 2005. A postal questionnaire was sent in February 2006 to 81 patients (no specific details of the questionnaire are given)and replies were received from 60 patients. In 56 of the replies the patient confirmed that they were taking co-proxamol in January 2005; 17 were still taking co-proxamol at follow up. Of the17 still on co-proxamol 6 had tried alternative analgesics. Of the patients who had changed from co-proxamol (39), 27 would choose to return to co-proxamol, 12 patients were content on the new analgesic. The authors conclude that in this selected group of patients co-proxamol provides significantly better pain relief than alternate analgesics. They suggest that more note should be taken of what are effectively *n* of 1 studies and that more patients should be allowed to continue to take what is the best drug for them.

Comment

Since no details of the questionnaire were given, the quality cannot be assessed. This was a very small sample size and may not be reflective of the population as a whole. The authors do not discuss the effect of leading questions in the questionnaire, nostalgia factors or dependency. This survey cannot be considered as scientific evidence.

[55] Ottewell L and Walker DJ 2008 'Co-proxamol: where have all the patients gone?' Rheumatology; 47: 375.

Sandilands and Bateman 2008[56] published a study showing that co-proxamol withdrawal has reduced suicide from drugs in Scotland. This was a retrospective observational study relating to poisoning by single agents in Scotland for the period 2000-2006.

A significant reduction in the proportion of poisoning deaths due to co-proxamol was observed following withdrawal. Previous studies had estimated that there was a minimum of 39 excess deaths each year in Scotland due to co-proxamol poisoning. The mean number of deaths in the period 2000-2004 was 37 deaths a year (21.8% of total poisoning deaths); in 2006, there were 10 deaths (7.8%); p<0.0001. The average number of deaths by age group in 2000-2004 was 12 in the 10-34 year age group, 17 in the 35-54 year age group and 9 in those older than 54 years. After the regulatory action there was a shift in the age distribution. In 2006 there was one death in the 10-34 year age group, 4 in the 35 to 54 year age group and 5 in those over 54 years of age. The decline in fatalities was associated with a decline in prescriptions by 60% within 6 months of regulatory action. There was no compensatory rise in mortality from other common analgesics accompanying the increase in the number of paracetamol and co-codamol prescriptions.

Deaths involving co-proxamol in a mixed overdose were excluded as it is difficult to establish the precise cause of death where more than one agent is involved.

Hawton et al 2009[57] published the results of a study investigating the effect of co-proxamol withdrawal on prescribing and deaths in England and Wales. The study was an interrupted time series analysis for 1998-2007.

Table 11: Effect of co-proxamol withdrawal in England and Wales

	Estimation of absolute effect during 2005 to 2007 after regulatory action[a]		
	Mean quarterly estimated number before action[b]	**Mean quarterly estimated number after action[b]**	**Mean quarterly change 2005 to 2007[c] (95% CI)**
Prescriptions (thousands)			
Co-proxamol	1465.1	605.7	-859 (-1065 to -653)
Cocodamol	2524.7	3024.6	500 (459 to 540)
Codeine	534.6	578.0	43 (31 to 55)
Codydramol	1018.2	1140.0	122 (99 to 145)
Dihydrocodeine	634.6	600.0	-35 (-68 to -2)
NSAIDs	5633.8	4581.0	-1053 (-1186 to -920)
Paracetamol	2947.0	3330.0	382 (268 to 497)
Tramadol	1130.1	1193.9	64 (-5 to 133)
Suicide, open			
Co-proxamol	39	15	-24 (-37 to -12)
Other analgesics[d]	39	44	5 (-5 to 15)
All drugs except co-proxamol and other analgesics	204	191	-13 (-34 to 8)
All drugs	283	252	-31 (-66 to 3)
All causes	1152	1130	-22 (-89 to 45)
Suicide, open, accidental			
Co-proxamol	48	19	-29 (-42 to -17)
Other analgesics[d]	56	60	4 (-11 to 18)
All drugs except co-proxamol and other analgesics	348	385	37 (-8 to 82)
All drugs	452	466	14 (-46 to 75)

a Using interrupted time series segmented regression analysis where the intervention point is taken as the end of 2004.
b Estimated for the midpoint quarter of 2005 to 2007.
c Absolute difference of estimated number with and without regulatory action taken at the midpoint of the post-intervention period.
d Cocodamol, codeine, codydramol, dihydrocodeine, NSAIDs, paracetamol and tramadol.

[56] Sandilands EA and Bateman DN 2008 'Co-proxamol withdrawal has reduced suicide from drugs in Scotland' Br J Clin Pharmacol 66: 290-3.
[57] Hawton K, Bergen H, Simkin S, Brock A, Griffiths C, Romeri E, Smith KL, Kapu N and Gunnell D 2009 'Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis BMJ 338: 62270

A steep reduction in prescribing of co-proxamol occurred in the post-intervention period 2005-2007. The analysis was restricted to deaths involving single drugs or single drugs and alcohol. The number of prescriptions fell by an average of 859 (95% CI 653-1065) thousand per quarter, equivalent to a decrease of about 59%. There was a concurrent decrease in prescribing of NSAIDs, equating to a 19% decrease overall for 2005 to 2007; and a decrease of 6% for dihydrocodeine prescribing. Prescribing of co-codamol, paracetamol, co-dydramol (dihydrocodeine/paracetamol) and codeine increased significantly during this time. These changes were associated with a major reduction in deaths involving co-proxamol with no statistical evidence for an increase in deaths involving other analgesics or other drugs. Between 1997 and 1999 co-proxamol was implicated in 766 deaths. The percentage of deaths due to co-proxamol alone before 2005 was 19.5% (95% CI 16.9-22.2); between 2005 and 2007 the figure was 6.4% (5.2-7.5).

Limitations of the study detailed by the authors included:

- Estimates of the overall effect on prescriptions and mortality involved extrapolation which is associated with uncertainty
- The regression method assumes linear trends with time and the co-proxamol data had a poor fit resulting in large standard errors in the post-intervention period
- Estimates of percentage changes over the three year post-intervention period are point-estimates, not determined with standard error calculations; therefore the percentage figures should be viewed with caution.

9.1 Summary of Effects on Restrictions on dextropropoxyphene

The data above show that restrictions on usage of dextropropoxyphene can reduce the number of deaths. However, education of prescribers cannot be left to commercial interests, as demonstrated by the US experience. It should be noted that a proper information and education campaign is expensive and needs to be repeated at regular intervals to be successful over time. Even then this may not be enough; in Denmark it appears that a central registry and monitoring of prescribers was required.

Withdrawal, either at a local level or national level, has been shown to reduce analgesic use and have a beneficial effect on suicide rates. The data published to date show that treatment with dextropropoxyphene was replaced with other analgesics, most commonly paracetamol alone, codeine alone or a codeine/paracetamol combination. Overall there was a decrease in suicide deaths.

Comparison of the safety profiles of dextropropoxyphene/ paracetamol and codeine/ paracetamol in the French Pharmacovigilance Database showed that codeine/ paracetamol had a better safety profile.

10 PARADEX MEDICINE UTILISATION STUDY

This study was commissioned by the sponsor for Paradex and performed by the New Zealand Pharmacovigilance Centre. Paradex was placed on the Intensive Medicines Monitoring Programme (IMMP) during the month of July 2007

The study consisted of two phases:

Phase one: An extract of all prescriptions dispensed was obtained to enable an initial analysis of prescribing practices (from Pharmhouse).

Phase two: IMMP study

A total of 43,473 scripts for patients across New Zealand who received a prescription in July 2007 were captured and entered into the IMMP database. Questionnaires were sent to a random selection of 1000 (from a total of 3370) prescribers to investigate the indications for use, severity

and chronicity of pain, and prior use of analgesic medicines. The total number of patients prescribed for by these 1000 prescribers was 5030.

Comment

The total number of patients receiving a prescription for Paradex in July 2007 was not clear, but appears to be 19387 in table12.

At the beginning of March 2008, 3039 questionnaires were sent to the individual patients prescribed Paradex by the 1000 randomly selected prescribers. 1628 questionnaires were returned; 1472 (48% of the questionnaires sent out) were assessable. Reasons for the questionnaires not being asssessable included: patient lost to follow up (4.7%), doctor lost to follow up (2.2%), returned blank (2.7%). It was noted that 36 patients had died since the prescription had been issued.

Comment

The return rate for questionnaires is very low and raises questions as to whether the IMMP cohort was truly representative of the population of patients taking Paradex.

The analysis of appropriate prescribing was based on adherence to the following criteria:

- Correct dose
- Pain severity in line with data sheet prescribing information
- Chronic Use
- Prior use and failure of other analgesics

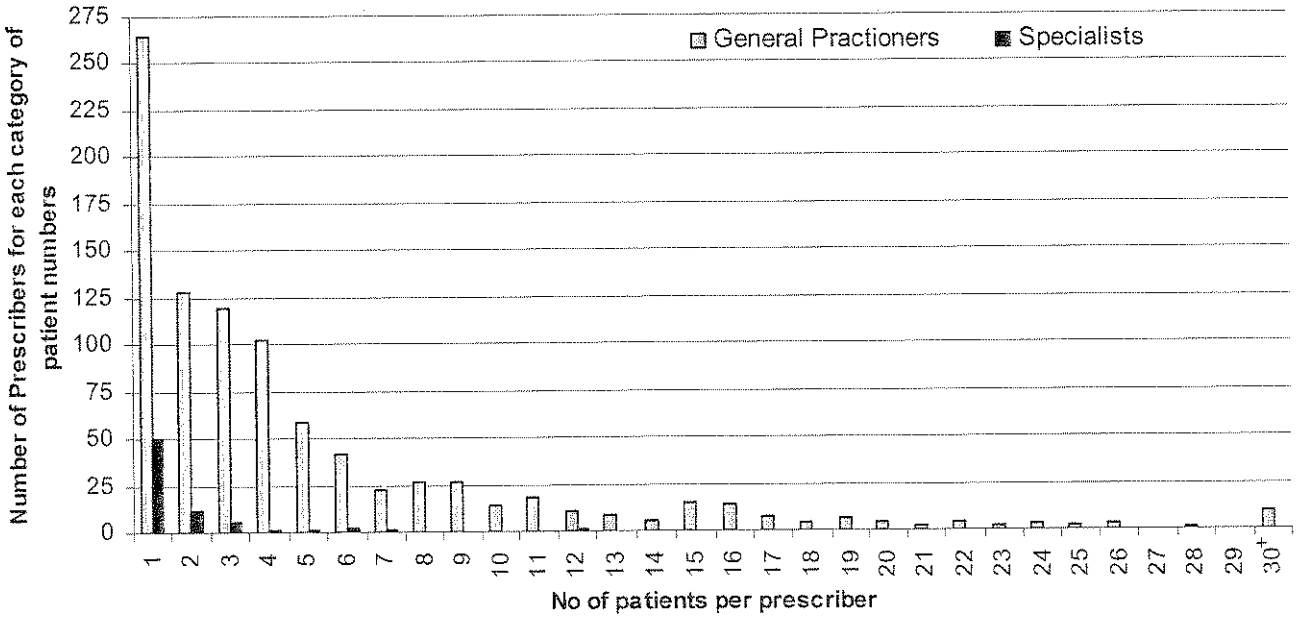

Figure 1: Number of patients prescribed Paradex per prescriber and prescriber type. In addition one dentist was noted to have prescribed Paradex for four patients. The 30+ category includes: three prescribers who each prescribed for 31 patients, two prescribers who each prescribed for 34 patients, one prescriber who prescribed for 38 patients, one prescriber who prescribed for 41 patients and one prescriber who prescribed for 56 patients.

An analysis based on clinical judgement of appropriateness of prescribing was also undertaken on the proportion for whom there was no evidence of disregard for the guidelines but the information was incomplete. Clinical judgement was recorded as a Pass or Fail. A pass was given in the following situations:

- If the prescription was incomplete regarding the dosage but the total amount prescribed was within the guidelines.
- If, for a patient on long-term therapy, the prescriber did not have access to records of previous medicines tried but other criteria were met.

The number of patients prescribed Paradex per prescriber in the randomly selected 1000 prescribers is shown in figure 1. The majority of prescribers were prescribing Paradex for three patients or less.

The age and gender distribution was analysed in both phase I and phase II of the study. Results are shown in Table 12 below.

Table 12: Comparative Age and Gender distribution of the Cohort.

	Phase 1 data from Pharmhouse			**IMMP Questionnaire Cohort**		
Age Group	**Female (% of total females)**	**Male (% of total male)**	**Total (% of total cohort)**	**Follow up of Female (% of total females)**	**Follow up of Male (% of total male)**	**Total Follow up (% of total cohort)**
0-9	12 (0.06)	11 (0.06)	23 (0.12)	0	0	0
10-19	145 (0.7)	103 (0.5)	248 (1.3)	30 (1.5)	17 (1.6)	47 (1.5)
20-29	379 (2.0)	218 (1.1)	597 (3.1)	61 (3.1)	41 (3.9)	102 (3.4)
30-39	811 (4.2)	474 (2.4)	1285 (6.6)	133 (6.7)	82 (7.7)	215 (7.1)
40-49	1402 (7.2)	836 (4.3)	2238 (11.5)	235 (17.7)	140 (13.3)	375 (12.3)
50-59	2146 (11.1)	1241 (6.4)	3387 (17.5)	352 (17.7)	186 (17.7)	538 (17.7)
60-69	2665 (13.7)	1552 (8.0)	4217 (21.8)	419 (21.1)	251 (23.9)	671 (22.1)
70-79	2679 (13.8)	1480 (7.6)	4159 (21.5)	369 (18.6)	208 (19.8)	577 (19.0)
80-89	2024 (10.4)	730 (3.8)	2754 (14.2)	302 (15.2)	97 (9.2)	399 (13.1)
90 plus	383 (2.0)	96 (0.5)	479 (2.5)	56 (2.8)	17 (1.6)	73 (2.4)
Unknown				28 (1.4)	13 (1.2)	42 (1.4)
Total	**12646 (65.2)**	**6741 (34.7)**	**19387 (100.0)**	**1985 (65.3)**	**1052 (34.6)**	**3039 (100.0)**

It should be noted that the IMMP cohort was not a subset of the Pharmhouse data, which includes only community reimbursed prescriptions.

Comment

It was noted that there were a number of prescriptions for children. It would have been helpful if further details on the cases included in the IMMP cohort had been discussed in the study report.

The returned assessable questionnaires (1472) were analysed for adherence to the prescribing criteria. The results are summarised in the following tables.

Table 13: Indication for use

Indication	**Number**	**Percentage (of 1472)**
Acute Pain	325	22.1
Chronic Pain*	1126	76.5
Other	3	0.2
Unknown	8	0.5
Not answered	10	0.7

*This category included patients where the indication was: recurrent pain usually migraine, acute and chronic pain or acute exacerbation of chronic pain.

Comment

The reason for the classification of patients with recurrent pain as chronic pain was not clear as these patients are unlikely to be taking Paradex on a continuous basis and this is not consistent

with the aims of the MARC recommended changes to the indication. The number of these patients is likely to be higher than 110 (migraine diagnosis in the table below), a change in classification would significantly affect the final results.

Table 14: Diagnosis

Diagnosis	Number (n=1665)*	Percentage (of 1472)
Injury	184	12.5
Overuse/Chronic pain	18	1.2
Musculoskeletal –non injury	165	11.2
Post operative	53	3.6
Back pain	218	14.8
Arthritis, inflammatory	73	5.0
Gout	14	1.0
Arthritis other	550	37.4
Nerve pain	94	6.4
Cancer pain	28	1.9
Migraine (headaches)	110	7.5
Other pain	153	10.4
Other – not pain	5	0.3
Not answered	25	1.7

*218 of the questionnaires indicated more than one diagnosis.

Table 15: Severity of pain

Severity	Number	Percentage (of 1472)
Mild	33	2.2
Mild to moderate	12	0.8
Moderate	1013	68.8
Moderate to Severe	54	3.7
Severe	328	22.3
Not answered	32	2.2

Table 16: Duration of treatment

Treatment Duration	Number	Percentage (of 1294)*
Less than 3 months	373	28.8
3 months to 6 months	53	4.1
6 months to 1 year	77	6.0
1 year to 2 years	83	6.4
2 years to 3 years	91	7.0
3 years to 4 years	81	6.3
4 years to 5 years	74	5.7
5 years to 10 years	204	15.8
10 years plus	70	5.4
Long term unspecified	188	14.5

*178 questionnaires did not provide an answer

Table 17: Previous treatment

Previous analgesic	Number	Percent of 946*
NSAIDs	461	48.7
Paracetamol	593	62.7
Paracetamol/codeine	133	14.1
Tramadol	50	5.3
Other opiates	108	11.4
Tricyclic antidepressants	62	6.5
Corticosteroids	21	2.2
Other CNS agents	12	1.3
Other	60	6.3

*946 questionnaires confirmed previous analgesic treatment, 314 confirmed no previous treatment, 163 were unknown. Of the 946 who had used another analgesic the reason for stopping was given as lack of therapeutic effect (45.5%), adverse reaction (20.8%), other (2%) and not answered (31.7%).

Table 18: Concomitant treatment

Concomitant CNS medicines	Number	Percent (of 1239)*
None	925	74.7
One	243	19.6
Two	51	4.1
Three	5	0.4
Five	1	0.1
Unknown	3	0.2
Not answered	10	0.8

* 1239 questionnaires indicated that the patient was taking other medicines, 16 of these indicated an overall excessive amount of paracetamol.

Table 19: Treatment continuation

Reason for stopping treatment	Number (n=519)*	Percentage (of 1472)
Lack of therapeutic effect	76	5.2
No longer necessary	354	24
Patient died	33	2.2
Adverse reaction	6	0.4
Other	20	1.4
Reason unknown	30	2.0

* Number of questionnaires indicating Paradex treatment had stopped.

The Paradex dose was considered by the medical assessor to be appropriate in 84.2 % of cases and not appropriate in 1.7%.

Assessment of appropriate use was made based on the response to questions on pain, severity, previous treatment and the appropriate dose. Using these criteria the use was appropriate in 46.3% of the cohort. Use was not appropriate in 1.5% (i.e. did not meet any criteria). Use was partially appropriate in 30.1% and could not be assessed in 22.2% of the cohort.

Using clinical judgement (as described above), use was considered to be appropriate in 63.2% and not appropriate in 36.5%.

Death was noted in 36 patients the cause of death was made through linkage with the NHI number. No suicides due to Paradex were noted and in most cases the cause of death did not appear to be related to Paradex use. Three patients died from respiratory disorders but there was no indication that respiratory depression was involved in the death.

Comment

Whilst the fact that the 36 deaths were not thought to be associated with dextropropoxyphene use may be considered to be reassuring, this was a small sample size from the total population of patients. The total cohort size from the Pharmhouse data was 19,387; therefore the IMMP analysable cohort was 7.6% of the total population. Usage data from Pharmac indicates that in 2007 the number of patients taking Paradex was 88,512; therefore the proportion of the total patient population analysed in this study was 1.7%. It should also be borne in mind that not all fatalities occur in patients prescribed dextropropoxyphene.

Limitations of the study as stated by the authors included:

- The short duration period of the study - 1 month
- The possibility that there was a difference between responders and non-responders to the questionnaire.

Comment

The results of this study indicate that, at the very least, education of prescribers about Paradex is needed. More investigation of the reasons for some GPs prescribing for more than 3 patients is warranted as is further investigation of prescribing for children.

11 DISCUSSIONS AND CONCLUSIONS OF OTHER REGULATORS

11.1 Summary of MHRA discussions on dextropropoxyphene

The risks and benefits of co-proxamol (usually dextropropoxyphene 32.5mg/paracetamol 325mg) were considered by the Committee on Safety of Medicines (CSM) and the Sub-Committee on Pharmacovigilance (SCOP) in 2004.

The CSM was asked to determine whether the risk benefit profile of co-proxamol was positive overall or whether there were any indications for which the risk benefit profile co-proxamol would be favourable.

In the UK at the time, co-proxamol was indicated for mild to moderate pain with a maximum daily dose of 8 tablets. It was noted that the product was toxic in overdose; as few as 10-20 tablets may be fatal. Death from overdose could occur within an hour and co-ingestion of alcohol or other central nervous system depressants significantly increased the risk.

Each year 300-400 people in England and Wales committed suicide or fatally overdosed with co-proxamol. Research at the time indicated that co-proxamol alone accounted for almost one fifth of drug-related suicides, second only to tricyclic antidepressants.

It was noted that co-proxamol had not been subjected to modern standards of clinical research. There had been no robust studies of greater than 48 hours duration. It did not meet the European criteria for a fixed combination product as there was no evidence of synergy between the active ingredients.

A review of efficacy showed that:

- For acute pain there was no robust evidence that co-proxamol had superior analgesic efficacy to full strength paracetamol
- For chronic pain (>48 hours) analgesic efficacy had not been demonstrated.

Prescribers had been repeatedly warned of the unproven efficacy and proven toxicity of co-proxamol for more than 20 years. Usage data indicated that it was still widely used in hospitals and was being prescribed by GPs for around 1.7 million patients annually.

Reasons for the use of co-proxamol were considered to include:

- extensive history of use
- custom and practice
- less constipating than codeine
- fewer GI effects than NSAIDs
- an unrealistic concern about the addictive potential of codeine compared with dextropropoxyphene
- pressure to prescribe analgesics perceived as more potent than paracetamol alone.

A survey of 30 UK teaching hospitals found that co-proxamol accounted for 35% of all issues of paracetamol-containing medicines. This was considered to have a major impact on the future prescribing habits of students and junior doctors.

Review of UK spontaneous adverse reaction reports revealed a total of 96 reports to dextropropoxyphene from 1st Jan 1995 to April 2004. This included reports of 19 deaths, 14 of which followed an overdose.

The Committee concluded that it was minded to advise that marketing authorisations for co-proxamol should be revoked. It recommended there should be a period of consultation seeking to uncover any as yet unidentified groups of patients for whom the risk: benefit balance of co-proxamol might be favourable.

The Committee considered the outcome of public consultation and an appeal by the marketing authorisation holders (MAHs) in November 2004. CSM considered that no new objective evidence had been identified and the MAHs had not satisfactorily addressed any of the points raised in a letter sent to them by CSM. Therefore the licences were revoked.

Comment

In the opinion of the sponsor for Capadex, the UK consultation process was poorly conducted. The CSM did not appear to take the views of the respondents into consideration. However, it should be noted that the CSM can only base its decisions on the scientific evidence, not opinions. At the time, a consultation on this type of issue was rather unusual in the UK.

11.2 Summary of FDA discussions on propoxyphene

The latest review of propoxyphene-containing medicines was sparked by a public citizen petition to the FDA requesting that these medicines be withdrawn from the market[58].

The petition states that propoxyphene has one of the most unfavourable benefit to risk ratios ever seen for a drug. As an example, the petition states that in 2007 in Florida there were 314 propoxyphene related deaths. In 85 cases the medical examiner concluded that the drug was a cause of death. In 66 of the 85 cases the death was judged to be accidental. The population of Florida is 18.7 million, around 1/16 of the total US population.

The petition states that propoxyphene has only weak analgesic effects. The most dangerous aspect of propoxyphene is the metabolite norpropoxyphene which is cardiotoxic and may cause QT interval prolongation leading to sudden death.

Reasons given for banning propoxyphene are:

- It is a dangerous drug: large amounts of propoxyphene are rapidly absorbed from the GI tract very quickly making attempted suicide difficult to treat.
- Even modest amounts of this drug can cause lethal cardiac arrhythmias in any individual with an undiagnosed hERG genetic polymorphism

[58] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/ucm129319.pdf.

- Use of propoxyphene can lead to toxic levels of antibiotics and anticonvulsants
- The drug is not particularly effective. For far less money, patients would get more pain relief if they took aspirin or acetaminophen.

The sponsors of propoxyphene submitted a briefing document to the FDA refuting the claims of the citizens petition[59].

The sponsors' document includes a reminder of the conditions under which a medicine may be removed from the market in the US. These are that the Secretary of the Department of Health and Human Services may withdraw approval of an application or abbreviated application for a new drug if he or she finds it presents an imminent hazard to public health. The FDA may withdraw approval after it determine that clinical or scientific data demonstrate the drug is unsafe under the conditions of use for which the product is approved and labelled or that there is a lack of substantial evidence from adequate and well-controlled studies that the drug will have the effect it purports to have under the conditions of use prescribed in its labelling.

The sponsor states that propoxyphene was first approved in the 1950s based on its safety. It underwent a second independent evaluation of efficacy in 1962. This evaluation found the drug efficacious in the treatment of mild to moderate pain. The product's safety and efficacy has been reaffirmed each time a new propoxyphene product was reviewed and approved by the FDA. Most recently a line extension was approved in 2003 and a generic version of the line extension in 2006.

The sponsor states that the petition does not raise any new safety or efficacy issues. Propoxyphene products have a long history of safe and effective use, as labelled, and are an essential option in the treatment of mild to moderate pain. As with all drugs there are risks associated with propoxyphene use, including deaths associated with overdose and concomitant use with drugs and/or alcohol and drug addiction. However, these risks have not prevented the safe use of propoxyphene in accordance with the approved prescribing information. The safe use is further safeguarded by its classification as a Schedule IV drug under the Controlled Substances Act.

The sponsor notes that the petition is inaccurate and misleading and does not present any legitimate scientific or clinical evidence that propoxyphene products are not safe or effective when used according to the approved labelling. The situation in the United States is considered to be different to that in the UK due to the differences in the propoxyphene salt used and the regulation of propoxyphene as a controlled substance.

Comment

The minutes of the Advisory Committee meeting[60] reveal that the Committee voted 14 to 12 to remove propoxyphene-containing products from the market. The Committee struggled to analyse the risk benefit profile as they felt that they didn't have information on the full range of possible side effects or comparative data with other medicines used for similar indications. There appeared to be little evidence that propoxyphene was markedly unsafe when used according to the licensed indications. In addition, the data on overdose deaths was not considered to support a problem with dextropropoxyphene. The FDA has not withdrawn the product but has taken regulatory action as outlined below.

[59] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM136518.pdf.

[60] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM120095.pdf.

12.0 DISCUSSION AND CONCLUSIONS

The difficulty of assessing the benefit risk profile of a medicine without good evidence of efficacy or safety is highlighted by the evidence presented for dextropropoxyphene and the conflicting views of other regulators.

Review of the efficacy of dextropropoxyphene-containing medicines concluded that these medicines have efficacy for post-operative pain. The data tends to suggest that neither dextropropoxyphene nor dextropropoxyphene/ paracetamol have superior efficacy to paracetamol alone.

No data was found to support the indication in New Zealand of chronic pain for dextropropoxyphene-containing medicines.

The review of safety concluded that the current data sheet information is inadequate. , Dextropropoxyphene appears to cause the typical side effects of opioids. In addition, there appear to be some notable additional adverse effects that include hypoglycaemia, hypersensitivity reactions, hip fracture, dependency and hepatic reactions.

It was noted that the number of deaths reported to the Poisons Centre had decreased. Although the review of the data on the safety of dextropropoxyphene in overdose showed that it is more toxic than other analgesics.

Since the efficacy studies indicate that dextropropoxyphene/ paracetamol has efficacy equivalent to paracetamol it is relevant to compare these medicines when judging the benefit risk balance. Clearly then, the benefit risk balance for dextropropoxyophene/ paracetamol is unfavourable as it causes qualitatively and quantitatively more adverse effects and is arguably more dangerous in overdose.

It should also be noted that in comparison with codeine/ paracetamol the benefit risk balance for dextropropoxyphene/ paracetamol is unfavourable for similar reasons.

No evidence was found that the benefit risk balance had changed significantly since the MARC last considered this issue.