MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 25, 2005

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Subject: **This is a revision of** the review of serious adverse events reported in association with propoxyphene and Darvocet® (propoxyphene/acetaminophen);NDA #s 10996, 10997, 16827, 16829, 16861, 16862, 16863, 16864, 76429, 17122, 16844, & 17507[1]

Confidential: Contains IMS data; not to be used outside of the FDA without clearance from IMS.

EXECUTIVE SUMMARY

Following an extensive review of the risk-benefit profile of the painkiller propoxyphene plus acetaminophen combination products in the United Kingdom, it was determined that the efficacy of this product "is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable." On January 31, 2005, the Committee on Safety of Medicines announced their plans to withdraw propoxyphene products from the market over a 6-12 month period.[1] In the U.K, the license of single-ingredient propoxyphene products were already cancelled.[2] Subsequently, Dr. Sharon Hertz from the Division of Antiinflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP) requested an AERS review of the serious postmarketing adverse event reports involving the use of propoxyphene products, with particular attention to deaths, suicides, overdoses, drug abuse, and dependence. Dr. Hertz also requested the IMS prescription drug use information for propoxyphene, as well as a review of other relevant national databases.

Given the short turn around time for this request, ODS agreed to provide the crude count analyses of all serious adverse event reports involving propoxyphene and a detailed review of the US death cases for Darvocet®. In the crude count analyses, we did not attempt to match the duplicate reports or perform individual case reviews of the adverse

[1] Review by same authors prior to revision dated March 24, 2005

event reports. Since individual reviews were not conducted, the information related to dose, duration, onset, history of drug abuse, and causality could not be assessed.

A total of 3075 (US-2186) serious adverse event reports for propoxyphene were identified in the AERS database from drug marketing (approved in 1957) to February 2, 2005. There was an increase in the crude counts of adverse event reports for propoxyphene from 161 in 1999 to 319 in 2004. It is important to note that these reports cited the use of the single ingredient propoxyphene products and/or the combination products containing propoxyphene. The most commonly reported adverse event terms were completed suicide, drug dependence, and drug overdoses, involving the co-ingestion of other medications including narcotics, alcohol, TCAs, SSRIs, and benzodiazepines. The serious outcomes included hospitalization (804), disability (51), life-threatening event (78), intervention required (75), and deaths (1160).

According to the IMS data, propoxyphene use was steady from 1994 to 1996. A slight increase occurred in 1997 with an estimated 31,589,000 prescriptions dispensed in the U.S. After 1998, a slight decrease was noted each year to roughly 26,899,000 prescriptions dispensed in 2004. The IMS data indicated that propoxyphene with acetaminophen (Darvocet®) was the most commonly dispensed formulation of propoxyphene.

There were a total of 91 US deaths associated with the Darvocet® use. The majority of the deaths were related to drug overdoses and suicides involving the co-ingestion of multiple medications. There were no consistent trends of hepatic failure or cardiac disorders including arrhythmias in the death cases. Of those 91 deaths, eight were not related to multiple drug overdoses. The reported adverse events (more than one event in some cases) included Cheyne-Stokes respiration (1), acute respiratory distress syndrome (2), acute respiratory failure/CHF(1), Torsades de Pointes/QT prolongation (1), thromboembolism (1), neuroleptic malignant syndrome (1), hepatic dysfunction (2), and hepatic/renal dysfunction (1). The direct causal role of Darvocet® in all cases could not be determined due to the underlying medical conditions and multiple co-suspect medications.

An analysis of data from the Drug Abuse Warning Network (DAWN) on the numbers of emergency department (ED) visits for both propoxyphene products and the comparator drug, hydrocodone was completed. The rate for ED mentions for propoxyphene ranged from 1.8 per 10,000 prescriptions sold in 1999 to 1.6 per 10,000 prescriptions sold in 2002. The rate for ED mentions for hydrocodone ranged from 1.9 in 1999 to 2.4 in 2002 per 10,000 prescriptions sold. Using the new DAWN data for 2004, the proportion of suicide attempts was found to be slightly higher for propoxyphene single drug only (13% of ED cases) than for hydrocodone single drug only (4% of all ED cases) and the proportion of overmedication was higher for propoxyphene single drug only (33% of all ED cases) than for hydrocodone single drug only (19% of all ED cases) as well. The proportion of propoxyphene only cases seen in the ED that required an ICU admission was similar to cases involving hydrocodone only and hydrocodone/APAP combinations but higher than for cases involving propoxyphene/APAP.

In a review of reports from the Toxic Exposure Surveillance System or TESS database for a five-year period, the overall number of calls to poison control centers concerning propoxyphene as single ingredient and combination product with acetaminophen exposures increased by about 11% from 5,680 in 1999 to 6,318 in 2003. While the total of propoxyphene-associated exposure calls increased by about 11%, the total number of fatalities in association with propoxyphene (single ingredient and combo with APAP) exposures declined by a half from 28 in 1999 to 14 in 2003. Overall, propoxyphene-associated fatalities represented about 1% of the total 1,106 fatalities that were reported in the TESS database in 2003.

Most of the propoxyphene-associated fatalities occurred in individuals who ingested multiple products. In 2003, all three single-ingredient propoxyphene-associated fatalities occurred in individuals who took multiple products simultaneously. In the remaining eleven fatalities in 2003 all but three occurred in individuals who took propoxyphene plus acetaminophen combination products only.

In conclusion, there was an increase in crude AERS counts of adverse event reports for propoxyphene from 161 in 1999 to 319 in 2004. However, since the most commonly reported events with propoxyphene were drug overdoses, dependence, and suicides involving the co-ingestion of multiple drug products, the significance of this observed increase for propoxyphene could not be established in this analysis. In addition, this increase in reporting could not be explained from the IMS drug use data since there was a steady decline in the total prescriptions dispensed during this period. The rate for ED mentions for propoxyphene from DAWN was stable and ranged from 1.8 per 10,000 prescriptions sold in 1999 to 1.6 per 10,000 prescriptions sold in 2002. Data from the TESS database confirms that propoxyphene products remain an important cause of morbidity and mortality in the U.S. From 1999 to 2003 there was an 11% increase in propoxyphene-associated exposure calls, but the number of fatal exposures with propoxyphene products declined by about 50%. In contrast, both the number of calls, and the number of deaths associated with hydrocodone products have increased in the timeframe data was available for this product. In 2001, there were 15,142 calls reported with hydrocodone and in 2003 there were about 19,538 calls, an increase by 29%. Similarly the number of fatal exposures with hydrocodone products increased by 68% from 47 in 1999 to 79 in 2003. The majority of these exposures occurred in individuals who reportedly took multiple products simultaneously with suicidal intent.

1. BACKGROUND

This memorandum is organized into a number of sections; a background, a review of an analysis of AERS reports, an analysis of data from Drug Abuse Warning Network, a summary of an analysis of Poison Control summary data, and a summary of the findings from these analyses.

Propoxyphene hydrochloride (Darvon-N®, Darvon Pulvules®) is a narcotic analgesic (C-IV) and was approved on 8/16/1957 for the relief of mild-to-moderate pain. Propoxyphene hydrochloride with aspirin and caffeine (Darvon Compound- 65®) is a narcotic analgesic combination (C-IV) and was approved on 11/12/1957 for the relief of

mild-to-moderate pain. Propoxyphene napsylate with acetaminophen (Darvocet N-50®, Darvocet N- 100®) is a narcotic analgesic combination (C-IV) and was approved on 12/19/1972 for the relief of mild-to-moderate pain. Multiple generic propoxyphene products are currently available in the U.S.

Safety concerns related to 1) propoxyphene's reported relative narrow therapeutic window (as discussed by S. Calderon, CSS in a memorandum to HFD-550 April 21, 2004) and 2) the hepatotoxicity associated with acetaminophen (in combinations including those with propoxyphene) that is a well recognized adverse event and has contributed to a significant number of acute liver failure cases in a few published studies[3,4].

The current labeling for the drug contains the following warning:

WARNINGS

- **Do not prescribe propoxyphene for patients who are suicidal or addiction-prone.**
- **Prescribe propoxyphene with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess.**
- **Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.**

Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. In a survey of deaths due to overdosage conducted in 1975, in approximately 20% of the fatal cases, death occurred within the first hour (5% occurred within 15 minutes). Propoxyphene should not be taken in doses higher than those recommended by the physician. The judicious prescribing of propoxyphene is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, propoxyphene should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs. Patients taking propoxyphene should be warned not to exceed the dosage recommended by the physician.

In 1980 there was a Congressional Hearing to address concerns about the abuse of propoxyphene. The Agency initiated an educational campaign in the late 1970s and early 1980s to reduce inappropriate prescribing of the product.[5]

2. DRUG USE[6]

Over 245 million prescriptions of propoxyphene tablets have been dispensed by retail pharmacies in the U.S between 1994 through 2004. The following table summarizes the projected total prescriptions of propoxyphene (Darvon®) and propoxyphene w/APAP (Darvocet®) dispensed by retail pharmacies (chain, independent, food store, and mail order, IMS NPA*Plus*™) in the U.S from 1994 to 2004. The drug use information listed below for propoxyphene (Darvon®) is not complete, since the drug was approved in 1957. It appears that the total prescriptions dispensed for propoxyphene peaked in 1998 (highlighted) with an estimated 31,951,000 prescriptions in the U.S. and had decreased each year to roughly 26,899,000 prescriptions dispensed in 2004.

Table 2.1. The projected total prescriptions of propoxyphene products dispensed by retail pharmacies from 1994 to 2004*

Drug	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Propoxyphene (total)	29,515	29,547	29,427	31,589	31,951	31,547	30,992	30,404	29,161	27,745	26,899
Propoxyphene (single ingredient)					971	938	870	819	795	690	657
Propoxyphene and APAP combination					30,706	30,375	30,375	29,927	28,234	26,959	26,163
Propoxyphene and other combinations					275	234	196	148	132	97	79

*** IMS NPA*Plus*™ Numbers are in thousands; ADD THREE 000's TO EACH FIGURE**

3. SUMMARY OF AERS ANALYSIS

3.1 OVERVIEW OF THE SERIOUS ADVERSE EVENTS WITH ALL PROPOXYPHENE PRODUCTS:

As of February 2, 2005, a total of 3075 adverse event reports for propoxyphene were identified in the AERS database, of which 2186 were domestic reports. It is important to note that these reports cited the use of the single ingredient propoxyphene products and/or the combination products containing propoxyphene.

The 30 most commonly reported adverse events were as follows (a report may contain more than one adverse event term):

Table 3.1 Top 30 Adverse Event Terms (Preferred Terms)

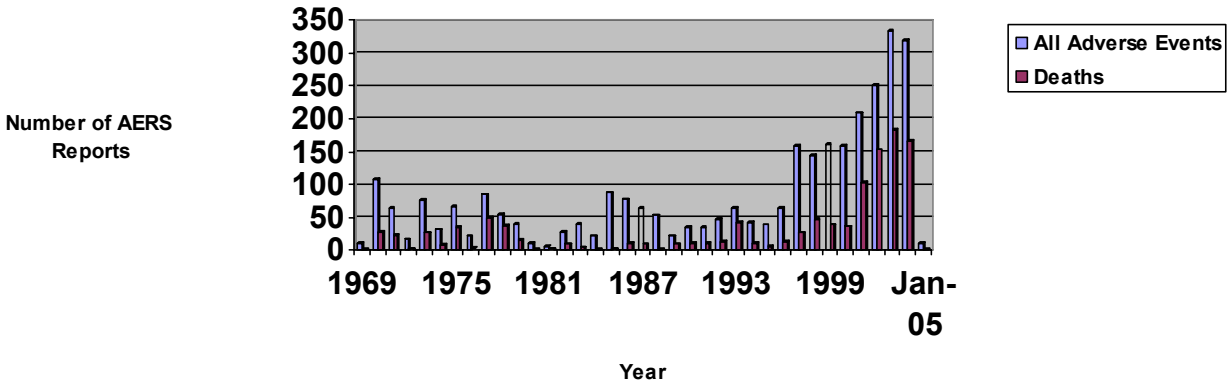
Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Intentional overdose	332		Sedation	80
Overdose	331		Confusional state	76
Completed suicide	228		Pruritus	72
Drug dependence	176		Asthenia	71
Coma	160		Death	71
Accidental overdose	146		Dermatitis	68
Nausea	131		Pulmonary oedema	66
Multiple drug overdose	123		Abdominal pain	65
Vomiting	119		Medication error	64
Convulsion	94		Dyspnoea	63
Drug toxicity	92		Hypotension	63
Drug ineffective	91		Pyrexia	62
Dizziness	90		Cardio-respiratory arrest	60
Drug interaction	90		Cardiac arrest	57
Drug level above therapeutic	83		Urticaria	57

The above table shows that the drug overdoses, suicides, and drug dependence were the most reported adverse events for propoxyphene in the AERS database.

Serious outcomes were reported in 2078 of 3075 reports, including 1160 deaths (US-950) and 804 hospitalizations. Other serious outcomes were coded as life-threatening (78), disability (51), congenital anomaly (14), and intervention required (75).

The following graph illustrates the number of reports received per year and the number of deaths per year, respectively. There appears to be an increase in the number of adverse event reports and the deaths reports related to propoxyphene from late 1999 to 2004. This increase in reporting could not be explained since there was a steady decline in total prescriptions dispensed during this period (See Table 2.1).

Figure 1. AERS Reports for Propoxyphene: All Adverse Events and Death Reports



The patient's gender was reported in 2644 of 3075 reports (M-1114, F-1530), and the age groups were as follows:

Table 3.2 Reported Age Groups

Age Groups	Counts for All Adverse Events	Counts for Death Reports		Age Groups	Counts for All Adverse Events	Counts for Death Reports
0 – <2 yrs	15	2		**41 yrs – 50 yrs**	484	254
2 yrs – 5 yrs	20	5		**51 yrs – 60 yrs**	323	131
6 yrs – 11 yrs	7	4		**61 yrs – 70 yrs**	246	72
12 yrs – 16 yrs	63	40		**71 yrs – 80 yrs**	255	55
17 yrs – 20 yrs	125	68		**81 yrs – 90 yrs**	133	21
21 yrs – 30 yrs	369	178		**91+**	20	4
31 yrs – 40 yrs	435	221		**Null age values**	579	105

The highest numbers of reports were in adults between 30 to 50 years. The adverse event cases consisted of expedited *{e.g. 15-day}* (1384), periodic (1255), direct (432), and risk assessor summary (3) reports.

The 30 most reported adverse event terms for the **U.S. cases of death** (950) associated with propoxyphene products were as follows:

Table 3.3 Top 30 Adverse Event Terms for U.S. Cases of Death

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Intentional overdose	226		Apnoea	27
Completed suicide	209		**Drug abuser**	27
Overdose	177		Hypotension	23
Accidental overdose	135		Brain oedema	22
Multiple drug overdose	106		Convulsion	22
Coma	81		Medication error	22
Drug toxicity	69		Drug interaction	19
Death	64		**Drug dependence**	17
Cardio-respiratory arrest	55		**Drug screen positive**	17
Pulmonary oedema	52		**Multiple drug overdose intentional**	16
Drug level above therapeutic	44		Depressed level of consciousness	15
Toxicologic test abnormal	42		Hepatic cirrhosis	13
Cardiac arrest	38		Multi-organ failure	13
Pulmonary congestion	30		Respiratory arrest	13
Cardiomegaly	28		Accident	12

The most reported adverse event terms from the U.S. death cases for propoxyphene are similar to the event terms for all propoxyphene cases (U.S./foreign/all outcomes) (See Table 3.1). It is interesting to note that the completed suicides and drug overdoses were the most frequently reported adverse event terms.

3.2 OVERVIEW OF THE SERIOUS ADVERSE EVENTS WITH PROPOXYPHENE /ACETAMINOPHEN (DARVOCET®)

As of February 2, 2005, a total of 490 adverse event reports for Darvocet® were identified in the AERS database, of which 472 were domestic reports. The 30 most reported adverse event terms were as follows:

Table 3.4 Top 30 Adverse Event Terms (Preferred Terms)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Overdose	46		Pain	18
Vomiting	43		Confusional State	17
Nausea	35		Myocardial Infarction	17
Coma	32		Pharmaceutical Product Complaint	17
Intentional Overdose	31		Hypotension	16
Dizziness	29		Pruritus	16
Dyspnea	29		Pyrexia	16
Drug Interaction	27		Abdominal Pain	15
Drug Level Above Therapeutic	23		**Complete Suicide**	15
Asthenia	22		**Drug Toxicity**	15
Medication Error	21		Fall	15
Sedation	20		Headache	15
Constipation	19		Weight Decreased	15
Liver Function Test Abnormal	19		Condition Aggravated	13
Drug Ineffective	18		Depression	13

The above table shows that the drug overdose was the most reported adverse event for Darvocet® in the AERS database.

Serious outcomes were reported in 353 of 490 reports, including 93 deaths **(US-91)** and 210 hospitalizations. Other serious outcomes were coded as life-threatening (21), disability (11), congenital anomaly (2), and intervention required (33).

The patient's gender was reported in 463 of 490 reports (M- 149, F- 314), and the age groups were as follows:

Table 3.5 Reported Age Groups

Age Groups	Counts for All Adverse Events	Counts for Death Reports		Age Groups	Counts for All Adverse Events	Counts for Death Reports
0 – <2 yrs	0	0		**41 yrs – 50 yrs**	57	20
2 yrs – 5 yrs	3	0		**51 yrs – 60 yrs**	72	23
6 yrs – 11 yrs	0	0		**61 yrs – 70 yrs**	46	4
12 yrs – 16 yrs	5	2		**71 yrs – 80 yrs**	77	8
17 yrs – 20 yrs	8	0		**81 yrs – 90 yrs**	43	4
21 yrs – 30 yrs	31	8		**91+**	4	0
31 yrs – 40 yrs	67	15		**Null age values**	77	9

The highest numbers of reports were in older adults between 30 to 80 years. The highest number of death reports were in adults between 40 to 60 years. The adverse event cases consisted of expedited *{e.g. 15-day}* (217), periodic (146), direct (126), and risk assessor summary (1) reports.

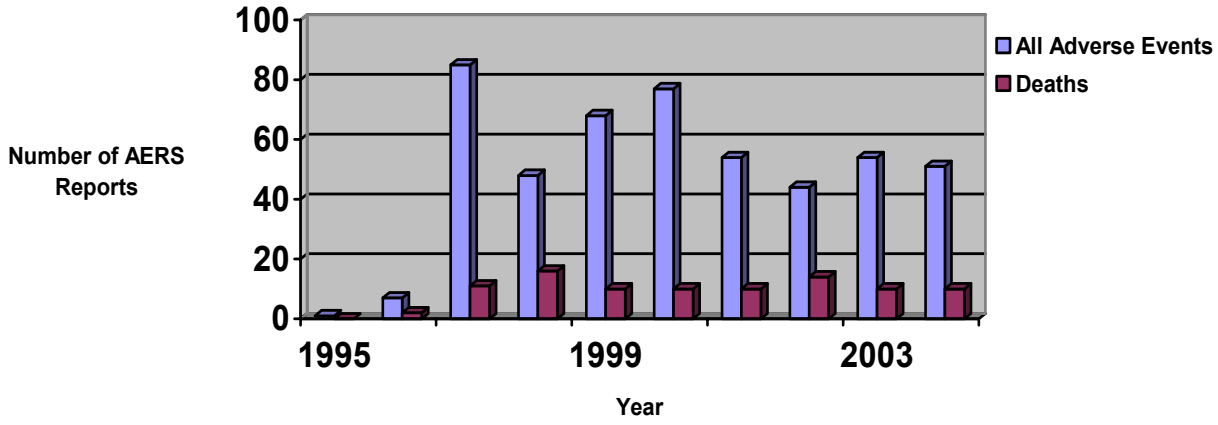
The 20 most reported adverse event terms for the **U.S. cases of death** (91) associated with Darvocet were as follows:

Table 3.6 Top 20 Adverse Event Terms for U.S. Cases of Death

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Overdose	**22**		Acute respiratory distress syndrome	7
Coma	**20**		Cardiac failure	6
Drug level therapeutic	**15**		Drug interaction	6
Completed suicide	**14**		Hypotension	6
Intentional overdose	**11**		Accidental overdose	5
Drug toxicity	9		Acidosis	5
Death	**7**		Cardiac arrest	5
Liver function test abnormal	7		Dyspnea	5
Multi-organ failure	7		Haematemesis	5
Sedation	7		Hepatic failure	5

The most reported adverse event terms from the U.S. death cases for Darvocet® (Propoxyphene /APAP) were similar to the event terms for all propoxyphene cases (U.S./foreign/all outcomes), primarily involving overdoses and suicides.

Figure 2. AERS Reports for Darvocet : All Adverse Events and Death Reports



The majority of the reports were drug overdoses, involving the co-ingestion of multiple medications including narcotics, TCAs, SSRIs, alcohol, narcotics, and benzodiazepines.

3.3 REVIEW OF U.S DEATHS UNRELATED TO INTENTIONAL MULTIPLE OVERDOSES OR SUICIDES WITH DARVOCET®:

Among 91 US death reports with Darvocet®, we identified 17 cases that appeared to be unrelated to multiple drug overdoses. Of the 17 reports, we excluded nine reports due to the following reasons:

- Carcinoma of the lung or breast with progressive metastatic disease (3)
- ARDS following chemotherapy and peg-filgrastim for lymphoma (1)
- Hepatic failure on Duract® (bromfenac) while alternating with acetaminophen (1)
- Guillain Barre Syndrome while receiving infliximab and methotrexate (1)
- Multi-organ failure and the use of 62 different medications, including 12 antibiotics in a patient with a h/o severe liver cirrhosis and renal failure (1)
- The adverse event was related to olanzapine (1)
- No information on the report (1)

The remaining 8 deaths involved 4 females and 4 males. The patient's age ranged from 21 to 77 years with a median of 55 years. The adverse events (more than one in some cases) preceding death were Cheyne-Stokes respiration (1), ARDS (2), acute respiratory failure/CHF (1), Torsades de Pointes (1), thromboembolism (1), neuroleptic malignant syndrome (1), hepatic dysfunction (2), and hepatic/renal dysfunction (1).

Seven of 8 cases reported significant underlying medical conditions (hypertension, COPD, severe gastrointestinal disorder and cardiac disease) and/or the use of multiple medications (carisoprodol, acetaminophen, erythromycin, domperidone, pergolide, nizatidine, omeprazole, prochlorperazine, baclofen, dantrolene, imipramine, metoclopramide, hydrocodone /APAP, olanzapine, and fluoxetine) that might have contributed to the reported adverse events. It is important to note that the concomitant use of acetaminophen and/or acetaminophen-containing products (Lortab® and Tylenol Flu®) in two cases might have contributed to the development of liver abnormalities. In another case, the concomitant use of erythromycin and domperidone and the patient's underlying gastrointestinal disorders may have contributed to the development of TdP and QT prolongation. The exact causal role of Darvocet® in all cases could not be determined.

A narrative of each case is presented below:

AERS# 1997177, US, Direct, 1997

A 33 year-old female with multiple drug allergies (sulfa, clarithromycin, NSAIDs) was receiving Darvocet® N-100 8 tabs daily (slightly higher than the recommended maximum daily dose of 6 tabs) for chronic pain and an unspecified dose of acetaminophen as needed for acute pain. After having a discogram, the patient received unspecified IV antibiotics and developed nausea and vomiting, which were treated with promethazine. She continued to have multiple episodes of nausea and vomiting during the day. She became very sleepy and combative after the procedure and was admitted to the hospital; she was subsequently intubated. The patient developed sepsis and ARDS, and died 10 days after the discogram. Pertinent lab values in the hospital included: AST 1150, ALT 1936, Alk Phos 250, GGT 244, total bili 15.3, albumin 2.9, and APAP 12 mcg/ml (interval unknown after the ingestion).

Reviewer's comments: It is not clear from the narrative whether the patient's liver abnormalities were due to an infectious process following the discogram, the use of the high dose acetaminophen (Darvocet® plus APAP), or both. The causal role of Darvocet® could not be determined.

AERS# 3057910, US, 15-day, 1998
A 36 year old male with a history of drug abuse/rehabilitation, hypertension, and chronic heart disease took 1-2 tablets of carisoprodol (Soma®) and 1-2 capsules of Darvocet -N® for chronic back pain. About 4-5 hours later, he demonstrated Cheyne-Stokes respiration and died. There was no evidence of drug or alcohol abuse at autopsy. The drug screen revealed only small quantities of diazepam, and meprobamate (metabolite of carisoprodol). Propoxyphene was not quantified.

Reviewer's comments: The underlying cardiac disease and/or additive effects of carisoprodol and Darvocet® on the respiratory system could have contributed to the respiratory depression. The causal role of Darvocet® could not be excluded.

AERS# 3430330 , US, 15-day, 1999
A 76 -year-old female patient with a h/o PUD, depression, acute pancreatitis, esophageal reflux, IBS, NIDDM, atypical Parkinson disorder, and back pain developed ARDS while she was receiving Prozac, Pergolide, nizatidine, Darvocet® (prn), omeprazole, and prochlorperazine. She was admitted to a hospital with a cough, pneumonia, dehydration, recent jaundice, and acute weight loss. She developed acute congestive heart failure with tachypnea and hypotension and died. The autopsy revealed bronchopneumonitis with mild ARDS, drug-induced cholestatic cholangitis, and mild hydrocephalus.

Reviewer's comments: The etiology of bronchial infection was unclear. The use of multiple hepatotoxic medications could have contributed to the liver injury. The role of Darvocet could not be determined.

AERS# 3683086 , US, 15-day, 2001
A 51-year-old paraplegic male with a h/o drug hypersensitivity (unspecified), muscle spasms, neurogenic bladder, COPD, and back pain received an unknown dose and duration of baclofen, dantrolene, Darvocet® and imipramine. He was recently treated with salbutamol, Atrovent, and metoclopramide for acute bronchitis. Within two days of the metoclopramide therapy, the patient became drowsy and more tachypneic. He developed an acute respiratory failure and congestive heart failure secondary to respiratory depression and died 3 weeks after the initiation of metoclopramide. The report mentioned that the patient had high levels of Darvocet (unspecified quantity) which was considered a co-suspect cause of the respiratory depression.

Reviewer's comments: It is possible that the high levels of Darvocet®, the patient's underlying COPD, and the acute bronchitis might have contributed to the respiratory depression.

AERS# 3907052 , US, 15-day, 2002
A 63 year old male with a history of insulin-dependent diabetes received an unknown dose of Darvocet-N® for pain and olanzapine for an unknown indication. He experienced neuroleptic malignant syndrome (NMS) and died. The autopsy results were not provided.

Reviewer's comments: The case did not provide sufficient information to evaluate the role of olanzapine or Darvocet®. Olanzapine product labeling includes NMS under the Warnings section. It is unlikely that the events were related Darvocet®.

AERS# 4021181, US, 15-day, 2002
A 59 -year -old female patient presented with hematemesis, epistaxis, chronic back pain, and a feeling of "doom". She received Darvocet® and/or Lortab® (hydrocodone bitartrate/acetaminophen) chronically for back pain and switched to Tylenol ES® (acetaminophen extra strength). She had also been taking Tylenol Flu® for cold symptoms. On admission the lab values were: ALT 3880, AST 1660, total bilirubin 4.9, INR 2.9, glucose 28, creatinine 2.2, pH 7.27, and APAP 19 mcg/ ml (interval unknown after the ingestion). She was treated with N–acetylcysteine, FFP, antibiotics, and hemodialysis. The blood cultures were positive for

E.Coli, methicillin- resistant staph aureus, and fungus. While the liver enzymes decreased, the total bilirubin (10 mcg/ml) and creatinine (9 mg/dl) increased. The patient continued to deteriorate and died.

Reviewer's comments: The concomitant use of multiple acetaminophen containing products (Darvocet®, Lortab® and Tylenol Flu®) might have contributed to the development of hepatic dysfunction. The contributory role of Darvocet® could not be excluded.

FDA 404851, US, 15-day, 2003
A 21-year-old female with a two year history of gastroparesis following a C-section and significant weight loss (100 lbs over 2 years, questionable eating disorder/depression) received Darvocet N -100®. The drug dose and duration were not reported. The concomitant medications included erythromycin (100 mg tid), fluoxetine (40 mg qd), and domperidone (10 mg tid). At an unspecified time after starting Darvocet, she developed severe epigastric/abdominal pain and vomiting, and was hospitalized. During her hospitalization, she was found unresponsive and developed Torsades de Pointes (QT/QTc: 429/492; 359/444; 240/351) and V-fib, requiring multiple cardioversions. Serum potassium levels were within the normal range. She died a day later and the autopsy determined the cause of death as myocardial infarction.

Reviewer's comments: The patient's long-standing gastric problems, profound weight loss, anorexia, and erythromycin and domperidone use might have played a role in the development of Torsades de Points and QT prolongation. The contributory role of Darvocet® was unknown.

AERS# 4269819, US, 15-day, 2004
A 77 year old male received two tablets of Darvocet N-100® to treat the pain from a broken leg. At an unspecified time after Darvocet® use, the patient experienced thickening and swelling of the tongue and difficulty eating and talking. He received Benadryl with some improvement followed by numbness. Seven days later, the patient developed a blood clot and died.

Reviewer's comments: This is the only death report that mentioned Darvocet® as the only primary suspect medication. However, the reporter did not provide any relevant clinical information including the underlying medical conditions, concomitant medications, and the patient's mobility status after the leg fracture to determine the possible cause of thrombosis in this elderly patient. The contributory role of the single dose of Darvocet® was unlikely.

4. ANALYSIS of DAWN DATA

This analysis focuses on data obtained from the Drug Abuse Warning Network (DAWN) on the numbers of emergency department (ED) visits. It compares numbers of ED mentions with drug use data from IMS Health™ for propoxyphene as well as for a comparator drug, hydrocodone, and computes the rate of DAWN emergency department drug mentions over drug usage data. Using more recent data, an analysis of the type of ED episodes or cases and the disposition of ED cases for propoxyphene and hydrocodone was also completed.

4.1 METHODS

This analysis utilizes the Drug Abuse Warning Network (DAWN) that is a public health surveillance system administered by the Substance Abuse and Mental Health Services Administration (SAMHSA). It monitors drug-related visits to hospital emergency departments (EDs). This analysis will use both "old" DAWN[7], data collected from 1994-2002 as well as "new" DAWN[8], that is data collected in 2003-2004.

Prior to 2003, data were collected on emergency room visits that involved drugs of abuse. Given that data were collected using a nationally representative sample, national estimates have been obtained for the number of ED mentions. A drug mention refers to a drug that was "mentioned" during a drug related ED episode or case. An ED case may involve up to 4 drugs and 55% of all ED cases involve more than one drug.

In 2003, a new, redesigned DAWN expanded beyond drug abuse to include all drug related ED visits. The new DAWN ED cases now consist of drug abuse and misuse, suicide attempts, overmedication, adverse reactions, accidental ingestions, malicious poisoning, underage drinking, patients seeking detoxification or drug abuse treatment. To date, only count information for the Years 2003 and 2004 can be obtained.

In the data, prior to 2003 all propoxyphene and hydrocodone mentions involve "drug abuse" cases only. That is, if a patient were to enter the ED for reasons that were not related to drug abuse or misuse; it would not be included in the DAWN data. In the DAWN data collected prior to 2003, it is not possible to ascertain how many cases involved other drugs and which drugs were present.

4.2 RESULTS

As noted in Table 4.1, the number of Narcotic Analgesic Emergency Department (ED) mentions overall has been on the rise from 1994-2004. The number of ED mentions for all narcotic analgesics for this time period rose 168%. However, the number of ED mentions for propoxyphene for the period 1994-2002 fell by 30%. The number of ED mentions during that same period for the comparator drug, hydrocodone rose 170%

Table 4.1: DAWN ED Mentions for the Coterminous US 1994-2002

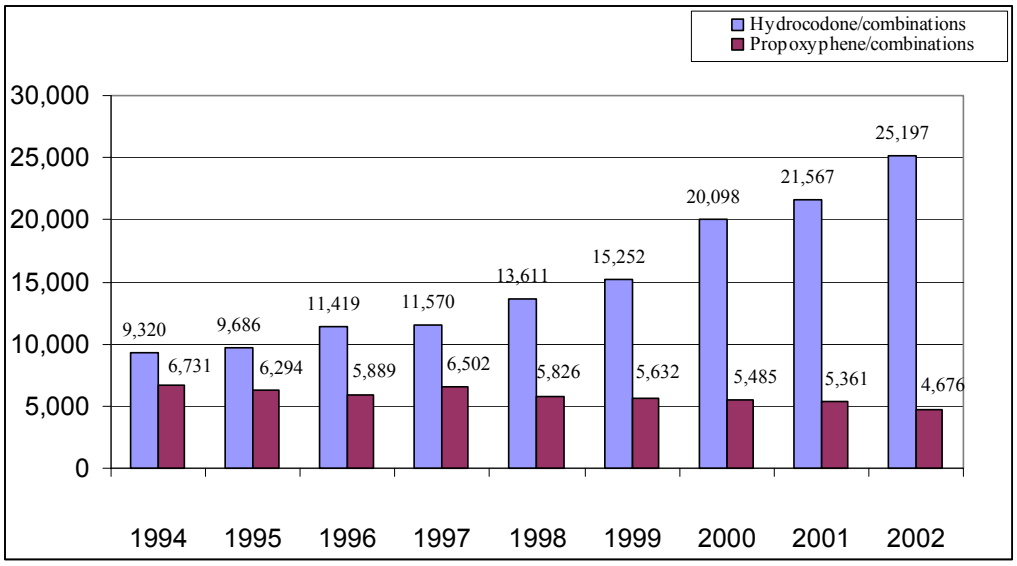
Drug name	*1994*	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*	*2002*	**% change** *1994 - 2002*
Narcotic analgesics/ combinations.	**44,518**	**45,254**	**46,941**	**54,116**	**58,946**	**69,011**	**82,373**	**99,317**	**119,185**	**167.7**
Narcotic analgesics	19,415	20,910	22,525	26,298	32,573	41,676	47,833	64,786	81,002	317.2
Narcotic analgesic combinations	25,102	24,343	24,416	27,819	26,373	27,335	34,540	34,531	38,183	52.1
Hydrocodone/ combinations	**9,320**	**9,686**	**11,419**	**11,570**	**13,611**	**15,252**	**20,098**	**21,567**	**25,197**	**170.4**
Hydrocodone	1,150	1,324	1,574	904	1,907	2,074	2,240	2,214	2,420	110.4
acetaminophen-hydrocodone.	8,168	8,362	9,845	10,667	11,686	13,043	17,538	19,058	22,227	172.1
Propoxyphene/ combinations	**6,731**	**6,294**	**5,889**	**6,502**	**5,826**	**5,632**	**5,485**	**5,361**	**4,676**	**-30.5**
propoxyphene.	1,515	1,068	1,065	1,166	1,109	816	593	684	492	-67.5
acetaminophen-propoxyphene.	5,216	5,224	4,822	5,337	4,714	4,816	4,891	4,675	4,168	ns

ns = not statistically significant

SOURCE: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002 (03/2003 update)[1].

In examining Figure 3, we can see that hydrocodone mentions are on the rise and that propoxyphene mentions are declining over time.

Figure 3: DAWN Estimates of ED mentions of Propoxyphene and Hydrocodone Products for the coterminous U.S. by Year



SOURCE: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002[1]

Although ED mentions for propoxyphene from 1994 – 2002 decreased and rose for hydrocodone, it is important to note that sales for propoxyphene also decreased and increased for hydrocodone as well. Therefore, in order to accommodate the differences in availability of the product, estimates for rate of ED mentions per prescriptions sold were computed. As seen in Table 4.2, the rate for ED mentions for propoxyphene ranged from 1.8 per 10,000 prescriptions sold in 1999 to 1.6 per 10,000 prescriptions sold in 2002. The rate for ED mentions for hydrocodone ranged from 1.9 in 1999 to 2.4 in 2002 per 10,000 prescriptions sold.

Table 4.2: Reporting Rate of Emergency Room Mentions for Projected Propoxyphene and Hydrocodone Sales

Drug name	1999	2000	2001	2002
DAWN Estimate of Total ED Mentions for Coterminous US				
Propoxyphene/combinations ED mentions	5,632	5,485	5,361	4,676
Hydrocodone/combinations ED mentions	15,252	20,098	21,567	25,197
IMS Health Projected Number of Total Prescriptions Dispensed				
Total Propoxyphene Sales[1]	31,547	30,992	30,404	29,161
Total Hydrocodone Sales[1]	81,725	88,778	96,318	103,645
Hydrocodone (minus cold/cough) Sales	68,802	76,631	83,216	90,261
ED Mentions Rate				
Propoxyphene Rate[2]	1.79	1.77	1.76	1.60
Hydrocodone (all) Rate[3]	1.87	2.26	2.24	2.43
Hydrocodone (minus cold/cough) Rate[3]	2.22	2.62	2.59	2.79

[1] (in thousands; add three 000's to each figure)
[2] Reporting Rate = ED Mentions/10,000 Prescriptions Sold
[3] Both hydrocodone reporting rates use total hydrocodone combinations as numerator
Source: IMS Health and Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2002 (03/2003 update)[1].

Given that most DAWN ED mentions involve use of multiple drugs, data were obtained that contained only single entity propoxyphene and hydrocodone and acetaminophen combinations that were reported in the DAWN data. Table 4.3 lists the proportion of the type of case reported for both single entity propoxyphene and hydrocodone and APAP combinations. The proportion of suicide attempts was higher for propoxyphene only cases (13% of ED cases) than for hydrocodone only (4% of ED cases). It was not effectively higher when comparing APAP combinations; where suicide attempts was 6% of ED cases involving propoxyphene/APAP than for hydrocodone/APAP combinations (5% of all ED cases). The proportion of over-medication was higher for propoxyphene only cases (33% of all ED cases) than for hydrocodone only (19% of all ED cases) as well. This relationship remained when comparing APAP combinations, but the differences were attenuated; where 24% of propoxyphene/APAP ED mentions were overmedications cases versus 22% for hydrocodone/APAP.

The proportion of cases seeking detox was lower for propoxyphene only and APAP combination (0 and 1% of all ED cases respectively) than for hydrocodone and APAP combinations (9% and 10% all ED cases respectively).

Table 4.3: 2004 Type of Case by Drug listed in DAWN ED Mentions*

Single Drug Entity DAWN cases	*Suicide Attempt (%)*	*Seeking detox (%)*	*Adverse reaction (%)*	*Over-medication (%)*	*Accidental ingestion (%)*	*Other (%)*
Propoxyphene n=40	5 (13)	0 (0)	18 (45)	13 (33)	1 (2)	3 (8)
Acetaminophen-Propoxyphene n=463	30 (6)	6 (1)	299(65)	112 (24)	3 (0.6)	13 (3)
Hydrocodone n=381	15 (4)	35 (9)	212 (56)	74 (19)	15 (4)	30 (8)
Acetaminophen-Hydrocodone n=2,795	139 (5)	279 (10)	1491 (53)	630 (22)	29 (1)	227 (8)

* Tables reflect cases that have been received by DAWN as of: 3/7/05. All DAWN cases are reviewed for quality control. Based on this review, cases may be corrected or deleted. Therefore, these data are subject to change. SOURCE: Office of Applied Studies, SAMHSA, New Drug Abuse Warning Network[8]

Given the low number of cases for propoxyphene only, it is difficult to compare the proportions of case disposition with the other drug classes. Bearing that in mind, Table 4.4 indicates the proportion of ED cases that were admitted to ICU/Critical care for propoxyphene only (8% of ED cases) was similar for cases involving hydrocodone only (9%) and hydrocodone/APAP combinations (7%). It was somewhat lower for propoxyphene/APAP cases (4%).

When examining the proportion of cases transferred to another hospital unit, the proportion of propoxyphene/APAP cases (4%) was lower than for the other three drug classes, propoxyphene only (13%), hydrocodone (13%) and APAP combinations (10%). It should be noted that the number of cases listed in table is lower than in Table 4.3 because the disposition for each case is unknown or has not been recorded.

Table 4.4: 2004 Case Disposition by Drug listed in DAWN ED Mentions*

Single Drug Entity DAWN Cases	*Discharged home/police (%)*	*Referred detox/trt (%)*	*Admit ICU (%)*	*Admit CD/detox (%)*	*Admit psych (%)*	*All other admit (%)*	*Transferred (%)*	*Died (%)*
Propoxyphene n=38	21 (55)	2 (5)	3 (8)	0 (0)	2 (5)	5 (13)	5 (13)	0 (0)
Propoxyphene /APAP n=446	334 (75)	4 (1)	19 (4)	1 (0.2)	15 (3)	56 (13)	16 (4)	1 (0.2)
Hydrocodone n=218	100 (46)	14 (6)	20 (9)	15 (7)	15 (7)	24 (11)	28 (13)	2 (0.9)
Hydrocodone/APAP n=1,831	936 (51)	99 (5)	121 (7)	103 (6)	170 (9)	215 (12)	182 (10)	5 (0.3)

* Tables reflect cases that have been received by DAWN as of: 3/7/05. All DAWN cases are reviewed for quality control. Based on this review, cases may be corrected or deleted. Therefore, these data are subject to change. SOURCE: Office of Applied Studies, SAMHSA, New Drug Abuse Warning Network[3]

It is important to note that given that the information provided are based on counts and are not weighted to reflect national estimates, therefore differences in the types of cases may not necessarily be generalizable nation-wide.

4.3 DISCUSSION

It is important to keep in mind the following limitation when making any conclusions about DAWN ED data. Most DAWN mentions of propoxyphene, as well as hydrocodone, included ED visits where other drugs were reported. As a result, it is not possible to attribute definitively the ED episode specifically to propoxyphene or the comparator drug, hydrocodone

Use of propoxyphene products appears to be going down as reported by IMS Health Prescription sales data. Simultaneously, decreases in absolute number of ED mentions in DAWN mentions have also been found for propoxyphene products. At the same time that does not mean that propoxyphene is without its risk. The warning already placed in the labeling is not without foundation. The proportion of ED cases that were admitted to ICU was somewhat higher for propoxyphene products than for hydrocodone products. In addition, the proportion of ED cases that listed suicide attempt or adverse reaction was higher for propoxyphene products than for hydrocodone products.

5. REVIEW OF TOXIC EXPOSURE SURVEILLANCE SYSTEM DATA

5.1 METHODS

The Toxic Exposure Surveillance System or TESS is a poisoning surveillance database maintained by the American Association of Poison Control Centers (AAPCC) in cooperation with 64 poison control centers in the U.S.[9] In 2003 (the latest year for which we have data), poison control centers linked with AAPCC served nearly the entire U.S. population of (294.7 million) including the 50 states, the District of Columbia, and Puerto Rico. Since 1983 when TESS was started, to the present time, this database contains 36.2 million potential human poison exposure cases including 2.3 million cases reported in 2003 alone.[10]

The AAPCC's annual reports from 1999-2003 were reviewed manually to determine the extent of poisoning in association with exposure to propoxyphene and hydrocodone products. Two tables in the annual reports (Table 21: Summary of Fatal exposures, and Table 22B: Demographic Profile of Exposure Cases by Generic Category of Substances and Products) were reviewed and formed the basis of this review. Every time propoxyphene or hydrocodone products were mentioned in the table they were included in the analyses.

Definitions and terminology used:

In the annual reports, '*Death*' is when a patient dies as a result of the exposure or as a direct complication of the exposure. Only those deaths that are probably or undoubtedly related to the exposure are coded in TESS.

The various reasons for exposure are defined here. '*Unintentional general*': all unintentional exposures. *'Suspected suicidal'* is defined as an exposure resulting from the

inappropriate use of a substance for reasons that are suspected to be self-destructive or manipulative.

'Health care facilities' include acute care hospitals, physician offices or clinics, and freestanding emergency centers. Nonhealth care facility refers to the site of exposure that is usually the patient's home.

5.2 RESULTS

Table 5.1 summarizes the total number of poisoning-related calls associated with propoxyphene and hydrocodone products. In the five-year review period, the overall number of calls to poison control centers concerning propoxyphene as single ingredient and combination product with acetaminophen exposures has increased by about 11% from 5,680 in 1999 to 6,318 in 2003. For hydrocodone plus acetaminophen combination product, the overall number of calls increased by about 29% from 15,142 in 2001 to 19,538 in 2003.

Table 5.1: Total Number of Poisoning-Related Calls to Poison Control Centers

Year	Propoxyphene Single ingredient	Hydrocodone Single ingredient	Propox+APAP Combo product	Hydrocod+APAP Combo product
1999	560	NA	5,120	NA
2000	561	NA	5,578	NA
2001	567	NA	5,853	15,142
2002	519	NA	6,018	17,386
2003	448	NA	5,870	19,538

Propox= Propoxyphene; APAP=Acetaminophen; Hydrocod=Hydrocodone; Combo=Combination
NA= Data not available

Table 5.2 summarizes the outcome of the total number of calls associated with propoxyphene and hydrocodone products referred to in Table 5.1. In 2003, of the total 6,318 calls that were received by poison control centers where propoxyphene products were involved 4,036 (or about 64%) were referred to a healthcare facility for treatment and 34% were unintentional exposures. Of the nearly twenty thousand hydrocodone plus acetaminophen-associated calls that were received in 2003, about 60% were treated in a health care facility and about 34% were unintentional exposures. When comparing propoxyphene /APAP combinations and hydrocodone/APAP combinations, the percent treated in a healthcare facility and that were unintentional were similar and the distribution was found to remain fairly consistent over the period where data was available.

Table 5.2: Outcome of Poisoning-related Calls – A. Number (%) Received Treatment in Healthcare Facility; B. Number (%) Unintentional Poisonings

Year	Propoxyphene Single ingredient Rx in HCF/ Unint		Hydrocodone Single ingredient Rx in HCF/Unint	Propox+APAP Combo product Rx in HCF/Unint		Hydrocod+APAP Combo product Rx in HCF/Unint	
1999	361(64%)	193(34%)	NA	3,295(64%)	1,824(35%)	NA	
2000	366(65%)	181(32%)	NA	3,691(66%)	1,915(34%)	NA	
2001	381(67%)	192(34%)	NA	3,717(63%)	2,006(34%)	9,030(60%)	5,123(34%)
2002	351(68%)	160(31%)	NA	3,840(64%)	2,123(35%)	10,541(61%)	5,672(33%)
2003	301(67%)	144(32%)	NA	3,735(65%)	2,014(34%)	11,683(60%)	6,625(34%)

Rx in HCF = Treatment in healthcare facility; Unint = Unintentional exposure; NA = Data Not Available

Table 5.3 summarizes the five-year comparison of fatal exposures associated with propoxyphene and hydrocodone single-ingredient products and their combination with acetaminophen product. The total number of fatalities in association with propoxyphene (single ingredient and combo with APAP) exposures declined by a half from 28 in 1999 to 14 in 2003. Overall, propoxyphene-associated fatalities represented about 1% of the total 1,106 fatalities that were reported in the TESS database in 2003.

Table 5.3: Fatal Exposures Reported to Poison Control Centers

Year	Propoxyphene Single ingredient	Hydrocodone Single ingredient	Propox+APAP Combo product	Hydrocod+APAP Combo product
1999	9	3	19	44
2000	5	2	23	43
2001	12	1	23	43
2002	7	12	28	65
2003	3	3	11	76

Propox = propoxyphene; APAP = Acetaminophen; Hydrocod= Hydrocodone; Combo= Combination

Most of the propoxyphene-associated fatalities occurred in individuals who ingested multiple products. In 2003, all three single-ingredient propoxyphene-associated fatalities occurred in individuals who took multiple products simultaneously; cocaine and olanzapine in one case, diphenhydramine and mirtazapine in the second case; and ibuprofen/oxycodone and zolpidem in the third case. In the remaining eleven fatalities in 2003 all but three occurred in individuals who took propoxyphene plus acetaminophen combination products only; in the other eight fatalities, additional products were ingested aside from propoxyphene plus APAP including single ingredient acetaminophen or in combination with other opioids, and aspirin.

The total number of fatal exposures with hydrocodone products (single and in combination with APAP) increased by about 68% from 47 in 1999 to 79 in 2003. Like propoxyphene-associated fatalities, in the case of hydrocodone-associated fatalities multiple products were ingested simultaneously. Overall, in 2003, hydrocodone-associated fatalities represented about 7% of the total 1,106 fatalities that were reported in the TESS database in 2003.

6. OVERALL DISCUSSION/CONCLUSIONS

This review includes a discussion of an analysis of AERS data for propoxphene products as well as an analysis of DAWN and TESS data comparing propoxyphene to hydrocodone product information. Conclusions from this analysis include the following:

AERS ANALYSIS

- A total of 3075 serious adverse events for propoxyphene were identified; 2186 of the cases were domestic,
- There was an increase in crude counts of adverse event reports for propoxphene from 161 in 1999 to 319 in 2004 (see Figure 1). However, since the most commonly reported events with propoxphene were drug overdoses, dependence, and suicides, involving the co-ingestion of multiple drug products, the significance of this observed increase for propoxphene could not be established in this analysis (tables 3.1 and 3.3)
- This increase in reporting could not be explained from the IMS drug use data since there was a steady decline in the total prescriptions dispensed during this period; of note the use of propoxyphene single ingredient product is especially low (see Table 2.1)
- The majority of the 91 US death reports for Darvocet® were related to overdoses and involved other medications as well.

DAWN ANALYSIS

- For the years 1999-2002, the propoxyphene emergency department mention rate (ED/prescriptions) from old DAWN remained stable, but the rate was higher and increased over time for hydrocodone (see Table 4.2)
- The three most common reasons for ED mentions in the new DAWN were adverse reaction , overmedication, and suicide attempt (see Table 4.3)
- The proportion of Propoxyphene only cases seen in the ED that required an ICU admission was similar to cases involving hydrocodone only and hydrocodone/APAP combinations but higher than cases involving propoxyphene/APAP.

TESS ANALYSIS

- For the years 1999 to 2003 there was a 11% increase in propoxyphene-associated exposure calls, but the number of fatal exposures with propoxyphene products declined by about 50%; both the number of calls, and the number of deaths associated with hydrocodone products have increased in the timeframe data was available for this product.
- Unintentional calls accounted for about 30% of calls for both propoxyphene hydrocodone calls; the percent of unintentional call did not change over time for either drug (see Table 5.2)
- The majority of propoxyphene-associated exposure calls occurred in individuals who reportedly took multiple products simultaneously with suicidal intent.
- Over 60 percent of calls for both propoxyphene hydrocodone calls were from patients that were followed-up in a healthcare (see Table 5.2)
- Overall, propoxyphene-associated fatalities represented about 1% of the total 1,106 fatalities that were reported in the TESS database in 2003; compared to 7% for hydrocodone-associated fatalities

In conclusion, a review of the information available to ODS suggests that propoxphene has been associated with serious adverse outcomes, often in relation to an intentional overdose. It is unclear if there has been a change over time in adverse events but two of three databases (AERS and TESS) suggest there may be some type of increase. The data available to the team to review did not provide enough information to determine if deaths could be related to propoxphene alone, acetaminophen in combination products, and/or co-ingestion of other psychoactive medications.

Although, there is limited information to guide any regulatory decision we provide the following considerations for further discussion:

- Given that propoxyphene product labeling already contains strong *Warnings* regarding excessive doses, either alone or in combination with other CNS depressants, strengthening the labeling alone (to possibly include a *Black Box Warning*) may not fully address the continued reports of inappropriate use of these products.

- All propoxyphene sponsors should consider implementation of an extensive education campaign focused on
  - patients (patient package insert/medication guide) to emphasize avoidance of propoxphene if they have a history of drug/alcohol abuse or dependence, or suicidal thoughts and other concerns as noted in the labeling
  - physicians (Dear Healthcare Letter) to emphasize appropriate patient selection emphasizing all risk factors including use of other interacting drugs, drug or alcohol abuse or a history of depression or suicidal behavior.

- Most importantly, given that there are published studies where investigators have reported that acetaminophen and narcotic combination products were a common cause of acute liver failure[3,4,11] and that the current review also indicates that propoxyphene plus acetaminophen combination products were possibly associated with continued reports of calls to poison control centers, ED visits, overdose, and suicidal attempts, the reformulation of propoxyphene/acetaminophen products should be considered
  - In the U.K., an extensive review of the data found "no robust evidence" that the 325mg of acetaminophen in propoxyphene combo product was "superior to full strength acetaminophen alone in either acute or chronic use".[1]
  - For any combination products that are not reformulated, consideration should be given to adding a precaution that some overdoses have occurred from patient unintentionally taking multiple acetaminophen products.

- There may be a need to further assess the risk benefit profiles of other pain relieving drugs (e.g., hydrocodone, and oxycodone) and their combination with acetaminophen.

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