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Subject:	Serious Adverse Events
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EXECUTIVE SUMMARY

This review is in response to a request from the Division of Analgesics, Anesthetics, and Rheumatology Products (DAARP) for an updated Adverse Event Reporting System (AERS), drug utilization, and published literature[i] review associated with propoxyphene containing products[ii]. A Citizen's Petition (CP) from Public Citizen's Health Research group (February 28, 2006) requested that FDA initiate a phased withdrawal of all propoxyphene-containing products "...because this drug has considerable human toxicity, addiction potential, abuse liability, but very limited therapeutic usefulness."[iii] The CP cited the phased withdrawal of propoxyphene-containing drugs by the UK due to poor benefit-risk ratio, a combination of "poorly established" efficacy and risk of toxicity. The CP also specified concerns for propoxyphene use in elderly patients and its potential for cardiovascular effects with overdosage. The CP request resulted in an Advisory Committee (AC) Meeting (January 30, 2009) to review the safety and the efficacy profile of this drug.

Regarding AERS data, a previously completed OSE postmarketing safety review of propoxyphene containing products (2005) is included in the background package for the upcoming AC Meeting in January 2009[iv]. Data from the 2005 review are referenced, for contextual purposes, in the updated AERS section of this document.

UPDATED AERS CASES (N=65)

The AERS database was searched for all U.S. serious reports of propoxyphene containing products from 1/1/2006 to 12/31/2007. (A prior OSE safety review[iv] [included in the background package] summarized AERS data from drug marketing [1957] to February, 2005). Sixty-five unique reports of serious adverse events were included in this case series to update the safety profile for the therapeutic[v] use of propoxyphene containing products.

A majority of the cases (51/65, 78%) reported the use of a propoxyphene combination product containing acetaminophen[vi], nine-percent of the cases (6/65, 9%) reported the use of a single ingredient propoxyphene, and the formulation used was unknown in twelve-percent of the cases (8/65, 12%). Cases with psychiatric (12) and cardiac (11) related events were most common, followed by drug ineffective (10), and multiple accidental drug

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[i] The literature review was focused on propoxyphene associated cardiotoxicity and the elderly population.

[ii] "propoxyphene containing products" refers to both single ingredient propoxyphene and combination with acetaminophen. No other combination products (e.g. aspirin) with propoxypene were reported in this case series.

[iii] Other safety issues raised in citizen's petition include inappropriate use by the elderly, drug ineffective, implicated in suicide, dependence, and abuse.

[iv] Recent OSE postmarketing review of propoxyphene and Darvocet®: Bonnel RA, Dormitzer C, Ahmad SR. Review of Serious Adverse Events reported in association with propoxyphene and Darvocet®, 7/25/2005 (AERS search date: 2/2/2005).

[v] Cases reporting "accidental overdose" were included in the detailed analysis

[vi] Drug strength was not specified (particularly the acetaminophen component) in a majority of the cases.

overdose (9). The remaining 23 cases varied widely; some were single reports with no particular pattern or notable characteristics. In some cases propoxyphene product was one of multiple co-suspect or concomitant medications either taken as needed, or as an on-going pain reliever; as such, its role could not be clearly assessed in these 23 cases[vii].

Sixty-five-percent (42/65) of the cases reported the use of concomitant medications. Most frequently reported CNS associated drugs concomitantly used with propoxyphene products were opioids (e.g. oxycodone and duragesic), psychotropics[viii], and benzodiazepines. Contributing factors[ix] (medical history or labeled medications) were reported in almost half (29/65, 45%) of the cases and unknown in 55% (36/65) of the cases.

In forty-percent (26/65) of the cases, patients were 65 years of age or older. A majority of these cases (20/26, 77%) reported underlying medical history or multiple co-suspect medications. However, propoxyphene containing products may have contributed to the events reported in the elderly population as temporal association (10/26, 38%) and positive dechallenge (4/26, 15%) were noted in some cases, particularly for psychiatric related events.

Almost all cardiac associated cases (8/11, 73%) reported contributing medical history including hypertension, chronic diastolic heart failure, cardiomyopathy, coronary artery bypass graft, atrial fibrillation, hypercholesterolemia, or use of concomitant medications labeled for cardiac related events. Propoxyphene products may have had additive effects in these cases but a direct causal role could not be determined given the contributing factors cited. In the remaining three cardiac cases (3/11), two were notable for drug interactions with metoprolol and duloxetine. The third case reported bradycardia in an 80-year-old male with a significant cardiac medical history and the use of concomitant medications labeled for cardiac events. However, based on a plausible temporal association (event onset after 2 days of starting the drug), propoxyphene may be associated with the bradycardia reported in this case. The remaining two cases also suggest propoxyphene could be associated with potentiating cardiac events through possible drug interactions.

Most of the fatal (8/12, 67%) cases involved accidental overdose with use of multiple drugs, including alcohol (3 of 8 cases). A direct causal role of propoxyphene products in these death cases could not be established given the multiple concomitant drugs (e.g. opioids, and benzodiazepines) and contributing medical history (included cardiomyopathy and history of drug abuse). Additive propoxyphene effects, however, could not be ruled out. The remaining four cases were cardiac related deaths implicating an overdosage of

[vii] There was one (1/23) case of a plausible drug interaction involving carbamazepine in a female patient of unknown age. Drug interaction with carbamazepine and propoxyphene is labeled in the current propoxyphene labeling.

[viii] Psychotropics: antidepressants, sedatives, and antipsychotics

[ix] Contributing factors refers to an underlying medical condition, past medical history or use of labeled concomitant medications that could have contributed to the reported adverse events.

propoxyphene products[x] (see sec. 3.1 for case details), two of which were also confounded by contributing medical history (cardiomyopathy and scoliosis).

LITERATURE REVIEW OF CARDIOTOXICITY

The Division of Epidemiology within the Office of Surveillance and Epidemiology reviewed the medical literature for evidence of an association between propoxyphene containing products and cardiotoxicity in humans.

We used PubMed and EMBASE to perform queries. We indentified a total of 16 publications for the final review, three of which described epidemiological studies. The remaining 13 publications consisted of case reports and a case series.

Of the three epidemiological study publications, two described randomized controlled studies examining cardiac effects with therapeutic dose of propoxyphene. One randomized study found no effect that could be attributed to propoxyphene. The other randomized study found a significant difference in one of the cardiac conduction abnormality measures. However, this difference did not translate to clinically significant cardiac function defects.

The third publication described two seperate observational studies evaluating cardiotoxicity outcomes in overdose patients. The prospective study found significant differences in cardiac conduction (prolonged QRS duration) on echocardiogram. The measures, however, were not clinically abnormal. The retrospective study found a significant correlation between QRS duration and propoxyphene concentration.

OVERALL CONCLUSIONS

- Propoxyphene products may have had additive effects that contributed to cardiac adverse events based on temporal association[xi] and positive dechallenge cited in some cases[xii].
- Propoxyphene products may have contributed to psychiatric adverse events given the temporal association[xiii] and positive dechallenge noted in some cases.
- Over one third of adverse event reports involving elderly patients (65 years or older) included psychiatric (e.g. hallucination, confusion, mental status changes) events that may reflect pharmacodynamic effects of propoxyphene in this population.
- Cases of drug interactions in this review suggest that propoxyphene taken concomitantly with certain drugs may be associated with increased concentrations

[x] The four death cases included drug interaction-1 (ISR # 5483387), documented over-ingestion in an autopsy report-1 (ISR # 5538276), and cases from an Annual Report of the American Association of Poison Control Centers-2 (ISR #'s 5223417 and 5280841).

[xi] Five cases reported the estimated onset from 3 hrs to 21 days from starting the propoxyphene product.

[xii] All three dechallenge cases reported bradycardia. Cardiac associated events in the five cases with temporal association were bradycardia-3 and tachycardia-2

[xiii] Estimated onset from day 1 of starting propoxyphene products: 2 doses to 14 days (n= 7)

of propoxyphene or the co-administered drug, resulting in potentially life threatening toxicity (including cardiac events).

- The increased risk of fatalities from overdosage when propoxyphene products are used in combination with opioids, benzodiazepines, antidepressants, or other CNS depressants noted in this review is reflected in the **WARNINGS section** of the current product labeling. However, a direct causal role in fatalities for therapeutically administered propoxyphene could not be established given the patients' underlying medical history, or use of multiple co-suspect drugs, or both, noted in a majority of the updated reviewed cases.
- The findings in the updated review of propoxyphene product associated events are qualitatively similar to the 2005 OSE Postmarketing Review. The direct causal role of propoxyphene containing products in both the 2005 and updated OSE reviews could not be determined based on the underlying medical conditions or multiple co-suspect medications.
- The top 20 event terms reported for serious U.S. cases (2006 to 2007) were qualitatively similar to the event terms reported for all U.S. cases reported from approval (1957) to 9/24/2008.
- Despite current propoxyphene label warnings, narcotic pain relievers and other CNS related drugs continue to be prescribed and used with propoxyphene containing products, including in elderly patients.
- Literature review revealed mostly anecdotal reports of propoxyphene-related cardiotoxicity and lacked sound scientific evidence to support an association between propoxyphene-contanining products and cardiotoxicity.
- In 2007, the majority of sales of single-agent and combination propoxyphene products were to retail pharmacy settings. The propoxyphene/APAP combination product is the most commonly dispensed to all age groups and is reflected in both the 2005 and this updated review.
- The trends for patient data (i.e., prescriptions received) were similar to prescription data (i.e., prescriptions filled).
- General Practice/Family Medicine/Doctor of Osteopathy physicians are the most common prescribing healthcare providers for all propoxyphene containing products.

RECOMMENDATION

Although serious adverse events, including death, many involving accidental and intentional overdosages with other, often multiple medications, continue to be reported with the use of propoxyphene containing products, the AERS data in this review are alone insufficient to substantially inform the question of phased withdrawal of propoxyphene containing drugs from the market requested in the Citizen's Petition. In OSE's opinion, the regulatory action recommended for FDA by the upcoming AC should be based on clear clinical evidence of propoxyphene efficacy satisfactory to inform a robust discussion of the risk/benefit profile for these drugs.

Should propoxyphene containing drugs remain on the market, we recommend consideration of additional regulatory action (e.g., strengthened labeling, or Risk Evaluation and Mitigation Strategies [REMS], or both) to address the ongoing concomitant use of these products with opioids, benzodiazepines, alcohol, and other problematic medications that continues despite current labeling precautions. Additionally, we recommend consideration of a post-marketing commitment for a clinical safety trial(s) should these products remain market approved.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Analgesics, Anesthetics, and Rheumatology Products (DAARP) for an integrated AERS update, drug utilization, and literature[xiv] review of propoxyphene containing products. A Citizen's Petition (CP) from Public Citizen's Health Research Group (2006) requested that FDA initiate a phased withdrawal of all propoxyphene-containing products based on its questionable efficacy and low margin of safety[xv]. The petition also expressed specific concerns for use in elderly patients and the potential for cardiovascular effects with overdosage. Pursuant to the CP, an Advisory Committee (AC) Meeting is scheduled for January 30, 2009 to review the safety and the efficacy profile of propoxyphene containing drugs.

Propoxyphene products were withdrawn from the Swiss market in 2003 and from the Swedish market in 2005 after a number of deaths were reported from accidental overdoses. The United Kingdom (UK) withdrew all propoxyphene containing products in 2007, after finding approximately 400 deaths due to overdoses, with one in five reported as accidental[xvi].

A previous detailed OSE review[xvii] of propoxyphene containing products (July 25, 2005) found a majority of the 91 U.S. death reports[4] naming Darvocet® (propoxyphene/APAP) were overdoses involving other medications in addition to propoxyphene containing products, or involved significant underlying medical conditions, or both. A direct causal role for propoxyphene/APAP in many cases, therefore, could not be determined.

[xiv] The literature review was focused on propoxyphene associated cardiotoxicity and the elderly population.

[xv] Other safety issues raised in the citizen's petition include inappropriate use by the elderly, drug ineffective, implicated in suicides, dependence, and abuse.

[xvi] Prescrire International February 2006, volume 15 (81)

[xvii] Recent OSE postmarketing reviews of propoxyphene and Darvocet®: Bonnel RA, Dormitzer C, Ahmad SR. Review of Serious Adverse Events reported in association with propoxyphene and Darvocet®, 7/25/2005 (AERS search date: 2/2/2005).

1.2 REGULATORY HISTORY

A total of 22 propoxyphene/APAP combination products and six propoxyphene (single ingredient) products are currently marketed in the US. Reference listed products are presented in the table below:

Table 1. **Products (RLD*) with propoxyphene/APAP combination**		
Formulation	Approval Date	Sponsor
Darvocet N-50 Tablets (50 mg propoxyphene napsylate and 325 mg APAP)	12/19/1972 *NDA 17-122	Xanodyne Pharm
Darvocet N-100 Tablets (100 mg propoxyphene napsylate and 650 mg APAP)	12/19/1972 NDA 17-122	Xanodyne Pharm
Formulation	Approval Date	Sponsor
Propoxyphene/APAP Tablets (65 mg propoxyphnene HCl and 650 mg APAP)	12/16/1996 *ANDA 40-139	Watson Labs
Products (RLD*) with propoxyphene as single ingredient		
Darvon Capsules (65 mg propoxyphene HCl)	8/16/1957 NDA 10-997	Xanodyne Pharm
Darvon-N Tablets (100 mg propoxyphene napsylate)	9/9/1971 NDA 16-862	Xanodyne Pharm

*Abbreviations: RLD-reference listed drug, NDA-new drug application, ANDA-abbreviated new drug application, APAP-acetaminophen

Approved indication (from current labeling):

- Darvocet: For the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever; 1-2 tablets every 4 hours prn
- Darvon: For the relief of mild to moderate pain; 1 tablet every 4 hours prn

1.3 PRODUCT LABELING[xviii]

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).

[xviii] http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=6075

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 sedative, 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.

PRECAUTIONS:

Drug Interactions—The CNS-depressant effect of propoxyphene is additive with that of other CNS depressants, including alcohol. As is the case with many medicinal agents, propoxyphene may slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of that drug. Such occurrences have been reported when propoxyphene was administered to patients on antidepressants, anticonvulsants, or warfarin-like drugs. Severe neuologic signs, including coma, have occurred with concurrent use of carbamazepine.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

To provide an overall postmarketing context for propoxyphene-related[xix] safety issues, U.S. adverse event reports were retrieved for the product's life-cycle (approved in 1957) up to September 24, 2008 (data lock date). A total of 3038 (serious and non-serious) adverse event reports were retrieved from the AERS database. This search result includes the AERS data from a prior (2005) OSE postmarketing review [xvi] and the updated AERS data

[xix] In this review propoxyphene containing products refers to: combination of propoxyphene/acetaminophen (Darvocet) or propoxyphene (Darvon). No other propoxyphene combination products were reported or specified in this case series.

covering 2006 to 2007. (These crude counts are presented under Results section 3.1, Tables 3 through 7).

2.2 UPDATED AERS SELECTION OF CASES

For this updated review, the AERS database was searched for all U.S. serious reports of propoxyphene containing products for the two years (1/1/2006 to 12/31/2007). Of the 192 U.S. serious adverse event reports retrieved from this search, 127 (127/192) reports were excluded from further analysis (see exclusion table for details). The remaining sixty-five (65/192) unique cases were included in this case series to provide a more accurate safety profile with the therapeutic[xx] use of propoxyphene containing products.

Table 2. Excluded Cases

Reasons for Exclusion	**N**
Duplicate reports	44
Completed suicides – Intentional	43
Intentional overdose/suicide attempt	11
Drug dependence/abuse/misuse	17
Homicide case	1
Event unlikely related to Propoxyphene/APAP	9
Medication error	1
Miscoded (foreign report)	1
TOTAL	**127**

2.3 LITERATURE REVIEW OF CARDIOTOXICITY

The literature search for cardiotoxicity identified a total of 124 articles for initial review. Of these studies only 3 epidemiological studies[1-3] and 13 case reports/series[4-16] met the selection criteria. There were no studies comparing elderly participants to younger subjects.

The publications were grouped according to propoxyphene dosage:

1. Propoxyphene taken in therapeutic dose
2. Propoxyphene taken in overdose

Studies published between 1960 and 2009 about propoxyphene and its cardiotoxic effects were identified through searches of PubMed and EMBASE using the following terms: cardiotoxicity, cardiac toxicity, cardiovascular risk, cardiovascular toxicity, cardiovascular side effects; combined with dextropropoxyphene [MESH]/adverse effects or toxicity or poisoning, norpropoxyphene, d-propoxyphene. Additional publications were identified from searching the cited bibliography of articles identified by the two databases. The term

[xx] Cases reporting "accidental overdose" were included for detailed analysis

"elderly" was added to the previous search terms in order to identify a subset of publications focusing on propoxyphene safety in the elderly. Publications were screened for inclusion in this literature review using the following criteria:

- Human studies
- Exposure propoxyphene product
- Information about cardiotoxic event outcome
- English version of publication available

Epidemiology studies that were not designed for the purposes of detecting cardiac events as the primary outcome or as an adverse event were excluded. For the purposes of this review a cardiotoxic event was defined as having a deleterious effect on the action of the heart due to abnormal activity of the cardiac muscle and/or its conduction system. Case reports have been included as well to provide a more complete view of the available evidence.

2.4 DRUG USE DATA

DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

The IMS Health, IMS National Sales Perspectives™ (see Appendix 1 for database descriptions) was used to determine the various retail and non-retail channels of distribution for single-agent and combination propoxyphene products. During year 2007, propoxyphene/APAP products accounted for nearly 90% of all propoxyphene sales.[xxi] Of the propoxyphene/APAP products, approximately 54% were sold toward retail pharmacy settings while about 31% and 14% were sold to non-retail and mail order channels, respectively. Retail pharmacy settings include chain, independent, and food stores with pharmacies, whereas non-retail pharmacy settings include non-federal hospitals, home health care, clinics, long-term care, federal facilities, prisons, universities, etc.

Single-ingredient propoxyphene products accounted for approximately 10% of overall propoxyphene sales. For these products, approximately 80% were sold toward retail pharmacy settings, 12% were toward non-retail pharmacy settings, and 8% were toward mail order settings.

Propoxyphene/asa/caffeine products accounted for less than 1% of the overall market of propoxyphene containing products. Retail distribution accounted for about 60% of sales and mail service distribution accounted for about 40% of sales during year 2007. In this analysis, we examined outpatient utilization patterns, excluding mail order.

DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions by product using SDI Vector One®: National (VONA) (see Appendix 1 for full description) for calendar years 2006-2007. We also examined the number of patients who received a prescription in the outpatient retail pharmacy setting using SDI Vector One®: Total Patient Tracker (TPT) for calendar years 2006-2007.

[xxi] IMS Health, IMS Nationals Sales Perspectives™, Data extracted 10-29-08. File: 0810prop.dvr

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that single-agent and combination propoxyphene products are distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

3 RESULTS

3.1 UPDATED AERS CASES

To provide an overall safety context for propoxyphene associated AERS reports, a search was performed from drug marketing (1957) to 9/24/2008 (data lock date). This search included the AERS data from a prior (7/2005) OSE postmarketing review of propoxyphene products[xvi]. A total of 3038 (serious and non-serious) U.S. adverse event reports for propoxyphene containing products[xxii] were retrieved.

For the updated crude count for serious events, an additional search was performed in AERS limited to all US reports of propoxyphene containing products from 1/1/2006 to 12/31/2007. This search produced a total of 192 US serious adverse event reports. A total of 127 (127/192) reports were excluded from further analysis (see Table 2 for details). Sixty-five (65/192) unique cases were included in this US case series and represent the most recent passive surveillance post-marketing safety profile for the therapeutic[xxiii] use of propoxyphene containing products.

The tables below summarize the 20 most frequently reported US adverse events (all types) for propoxyphene containing products over all marketed years since initial approval (data lock date 9/24/2008). The AERS search results totals were: serious and nonserious reports, n=3038; serious reports, n=2136; and death as an outcome, n=1452. (It is important to note these results are crude counts only. Additionally, the crude counts may contain duplicate reports and the events may not necessarily be associated with propoxyphene containing products).

The adverse event terms bolded in the tables below are terms found in both the 2005 and this updated review and are generally representative of the most frequently reported adverse event terms since initial product approval.

[xxii] Propoxyphene containing products includes:

[xxiii] Cases reporting “accidental overdose” were included for detailed analysis

AERS CRUDE COUNTS

The most frequently reported event terms from approval (1957) to 9/24/2008 were overdose, including intentional, multiple drug, or accidental overdoses, followed by completed suicides, drug dependence and cardiac arrest. These are summarized in Table 3, below.

Table 3. Top 20 Adverse Event Terms (U.S. All Events, n=3038; marketing [1957] to 9/24/2008)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**433**		Nausea	122
Intentional Overdose	**341**		Respiratory Arrest	109
Overdose	**319**		Vomiting	107
Multiple Drug Overdose	**191**		**Cardio-Respiratory Arrest**	**104**
Drug Dependence	**168**		**Death**	**98**
Cardiac Arrest	**161**		Dizziness	98
Accidental Overdose	**159**		**Drug Interaction**	**94**
Coma	154		Convulsion	79
Drug Ineffective	**130**		**Confusional State**	**75**
Drug Toxicity	**126**		Dizziness	98

Serious outcomes were reported in 2136 of the 3038 reports from approval to 9/24/2008. The most frequently reported adverse event terms in Table 4 (below) were similar to those in Table 3 (e.g. overdose of any type, completed suicide, cardiac arrest, and drug toxicity).

Table 4. Top 20 Adverse Event Terms (U.S. Serious Events, n=2136; marketing [1957] to 9/24/2008)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**433**		**Death**	**98**
Intentional Overdose	**303**		**Drug Interaction**	**75**
Overdose	**286**		Pulmonary Oedema	74
Multiple Drug Overdose	**191**		**Multiple Drug Overdose Intentional**	**68**
Accidental Overdose	**156**		Vomiting	64

Cardiac Arrest	**153**		Drug Level Above Therapeutic	63
Drug Toxicity	**125**		Hypotension	63
Coma	122		Nausea	62
Respiratory Arrest	108		**Suicide Attempt**	**59**
Cardio-Respiratory Arrest	**104**		Dyspnoea	58

The AERS database was searched for death as an outcome which retrieved a total of 1452 reports from marketing (1957) to 9/24/2008[xxiv]. The most reported adverse event terms for the U.S. death cases (refer to Table 5, below) were similar to the event terms for all propoxyphene cases (serious and nonserious) including completed suicides and overdose or intentional overdose.

Table 5. Top 20 Adverse Event Terms (U.S. Deaths, n=1452; marketing [1957] to 9/24/2008)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**433**		Coma	96
Intentional Overdose	**282**		Pulmonary Oedema	70
Overdose	**255**		**Multiple Drug Overdose, Intentional**	**67**
Multiple Drug Overdose	**173**		Drug Level Above Therapeutic	49
Accidental Overdose	**152**		Pulmonary Congestion	45
Cardiac Arrest	**148**		Toxicologic Test Abnormal	43
Drug Toxicity	**117**		Hypotension	41
Cardio-Respiratory Arrest	**103**		**Drug Abuser**	**40**
Respiratory Arrest	102		**Intentional Drug Misuse**	**40**
Death	**98**		**Suicide Attempt**	**39**

[xxiv] Note the 91 death cases reported in a prior 2005 OSE Review were associated only with trade name Darvocet (search dates from 1957 to 2/2/2005). The updated review included both the trade and generic propoxyphene containing products to search the database which retrieved a total of 98 death reports for the two years (2006 to 2007).

For an updated comparison of top adverse event terms, an additional search was performed in the AERS database for updated serious (Table 6) and death cases (Table 7) limited to the two years (1/1/06 to 12/31/07).

Table 6. Top 20 Adverse Event Terms (U.S. Serious Events, n=192; 1/1/2006 to 12/31/2007)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**50**		Hyponatraemia	10
Cardiac Arrest	**24**		Bradycardia	9
Respiratory Arrest	21		**Intentional Overdose**	**9**
Dizziness	17		Loss of Consciousness	9
Intentional Drug Misuse	**16**		**Overdose**	**9**
Drug Toxicity	**15**		**Confusional State**	**8**
Drug Interaction	**14**		Fall	8
Somnolence	14		Hip Fracture	8
Cardio-Respiratory Arrest	**12**		Pain	8
Drug Abuser	**11**		Vomiting	8

A total of 192 U.S. serious cases were retrieved from the AERS database, and the top event terms are presented in Table 6. These top 20 adverse event terms were a fair representation of the adverse event terms reported for all U.S. cases from approval to 9/24/2008. Completed suicide, cardiac arrest, and intentional drug misuse were the most reported terms.

For the updated crude counts, AERS was searched for all propoxyphene containing products with death as an outcome from 1/1/2006 to 12/31/2007. A total of 98 death reports[xxiii] were retrieved and the top 20 event terms reported in these reports[xxv] (Table 7 below) followed a consistent trend as the U.S. cases for serious and nonserious events reported for all years of propoxyphene product marketing to 9/24/2008. Completed suicide and cardiac arrest were most reported terms.

Table 7. Top 20 Adverse Event Terms (U.S. Deaths, n=98; 1/1/2006 to 12/31/2007)

Preferred Term (PT)	PT Counts		Preferred Term (PT)	PT Counts
Completed Suicide	**50**		**Death**	**6**
Cardiac Arrest	**23**		Dehydration	6
Respiratory Arrest	20		**Drug Abuser**	**6**
Intentional Drug Misuse	**15**		**Overdose**	**6**
Drug Toxicity	**14**		Aortic Valve Calcification	5
Cardio-Respiratory Arrest	**12**		Cardiomegaly	5
Somnolence	8		Hepatic Steatosis	5
Intentional Overdose	**7**		Pulmonary Oedema	5
Pulmonary Congestion	7		Spleen congestion	5
Vomiting	7		Asthma	4

[xxv] Note: A report may contain more than one preferred (PT) event term.

Updated AERS Cases of Serious Adverse Events (N=65)

From 1/1/2006 to 12/31/2007 there were 65 unique U.S. reports of serious events with propoxyphene containing products found in AERS and included for this review. The demographic characteristics and the narrative of representative cases are described in Table 8, below.

Table 8. Demographics and other parameters of U.S. Serious cases reported with propoxyphene containing products from 1/1/2006 to 12/31/2007 (N=65)

Age (yrs): n=53	Range: 19-92 (median-62)
Gender:	Female (42), Male (21), Not reported (2)
Drug product[xxvi]: n=57	Propoxyphene/acetaminophen (51), propoxyphene (6)
Indication for use: n=31	Pain (unspecified) (13), ankle pain (1), back pain (6), dental/surgical pain (3), joint/hip pain (3), leg/knee pain (2), osteoarthritis (2), nerve pain (1)
Total daily dose: n=13	Range 100 mg – 800 mg (median-200 mg)
Estimated time of onset[xxvii]: n=18	Range 1 dose to 4 years (median-1 day)
dechallenge[xxviii]	Positive (8)
Estimated duration of therapy: n=16	Range 1 day to 16 years (median-15 days)
Outcome*	Death (12), Hospitalization (29), Life-Threatening (5), Other {medically significant} (38)
Report type	Expedited (38), Direct (18), Periodic (9)
Reporter: n=58	Physician (15), Pharmacist (8), Other Health Care Professionals (18), Attorney (2), Consumer (15),

*A case may have more than one outcome

[xxvi] "Propoxyphene product" in this review refers to both single ingredient propoxyphene and propoxyphene combination with acetaminophen.

[xxvii] Time to onset from day 1 of starting the drug

[xxviii] Rechallenge cases-none

The reported adverse events possibly associated with the propoxyphene containing products were categorized according to the AERS system organ classes (SOC) as listed below (a given report may contain more than one adverse event term):

System Organ Class (14): Preferred Terms (n)

Cardiac disorders: arrhythmia (1), bradycardia (6), cardiac/respiratory arrest (3), congestive arrest (3), congestive heart failure (CHF), tachycardia (2), myocardial infarction (MI) (1)

Eye disorder: eye swelling (1), vision blurred (1)

General disorder and administration site conditions: drug ineffective (10), drug ineraction (5), drug intolerance (1), influenza like illness (1), injection site bruising (1), drug withdrawal syndrome (1)

Gastrointestinal disorder: gastrointestinal bleed (1), acute pancreatitis (1)

Hepatobiliary disorder: hepatic steatosis (1), hepatomegaly (1), hepatocellurlar injury (1)

Immune system disorder: hypersensitivity (2)

Injury poisoning and procedural complications: drug toxicity (1), hip fracture (1), multiple drug overdose[xxix] (11), narcotic overdose[1] (1)

Investigations: blood pressure decreased (3), heart rate elevated/abnormal (4)

Metabolism and nutrition disorder: metabolic acidosis (1)

Nervous system disorder: ataxia (1), cerebral haemorrhage (1), coma (1), dizziness (2), somnolence (1), syncope (1)

Psychiatric: abnormal behavior (1), confusional state (3), hallucinations (5), mental status change (6)

Respiratory, thoracic and mediastinal disorders: respiratory depression (1), dyspnoea (1)

Skin and subcutaneous tissue disorder: rash (1), itch (1)

Social circumstances: abortion induced (1)

[xxix] These overdose events were reported as accidental (7) or they were unintentional overdoses (4) based on the descriptions in the narratives.

Clinically significant and other selected events of interest are grouped and summarized in greater detail as follows:

Cardiac Related Event Cases (N=11)

Eleven cases reported cardiac related events (arrhythmia -1, bradycardia[xxx]-4, cardio-respiratory arrest-2, congestive heart failure-1, myocardial infarction-1, tachycardia-2). Almost all cases (9/11, 82%) also reported contributing medical history including hypertension, chronic diastolic heart failure, cardiomyopathy, coronary artery bypass graft, atrial fibrillation, hypercholesterolemia, or use of concomitant medications labeled for cardiac related events. This information was unknown in two (2/11) cases. In most cases (8/11, 73%), another drug was reported as the primary suspect drug (fioricet, diphenhydramine, duloxetine, donepezil, vicodin, pregabalin, infliximab, and rofecoxib). In the remaining three cases (3/11), propoxyphene was listed as the primary or co-suspect drug, and two of these cases reported notable drug interactions, while the third case reported bradycardia in an 80-year-old male using multiple concomitant medications for various associated medical conditions.

Summary of the 3 notable cases (includes one literature report[xxxi]):

The first case involves a 48-year-old male with life-threatening bradycardia who was concomitantly taking 100 mg metoprolol and 200 mg propoxyphene napsylate with 1300 mg acetaminophen. Metoprolol was his usual maintenance drug for atrial fibrillation and the propoxyphene/acetaminophen was newly added as a post-operative pain medication[xxxii]. At the time of the event, the patient's heart rate dropped to 30 to 40 beats per minute; he was subsequently discharged with a heart rate (HR) of 70 beats per minute.

The second case involved a 61-year-old female with a medical history of cardiomyopathy. The only two reported drugs were duloxetine and propoxyphene. Cardiac arrhythmia was reported as the immediate cause of death. No other drugs were detected during the postmortem analysis.

These first two cases plausibly represent drug interactions: the CYP450 effects of propoxyphene may be associated with the cardiac events of bradycardia and arrhythmia based on its pharmacological properties when used with other (e.g. metoprolol and duloxetine) drugs also involved in this CYP450 pathway (see representative cases for details).

In the third case an 80-year-old male patient was hospitalized for bradycardia and low blood pressure two days after taking propoxyphene (dose and duration of use unknown) every 6 hours for dental pain. Contributing medical history included coronary artery disease, chronic diastolic heart failure, and aortic valve stenosis. Possible contributing

[xxx] One case was coded as bradycardia and drug interaction

[xxxi] Marraffa J, Lang L, et al. Profound metoprolol-induced bradycardia precipitated by acetaminophen-propoxyphene. Clinical Pharmacology & Therapeutics: 79(3):282-286, March 2006.

[xxxii] Patient underwent umbilical hernia repair. Other concomitant medications included diltiazem, atorvastatin, levothyroxine, fosinopril, amitriptyline, warfarin.

concomitant medications included felodipine, atenolol, and lisinopril (bradycardia is a labeled event in these three drugs). The event resolved after the propoxyphene product was discontinued and the patient was discharged with instructions to take only acetaminophen for pain if needed. In this case, bradycardia and low blood pressure resolved after treatment with atropine and dopamine; the event did not recur during the hospital stay (propoxyphene was discontinued). Propoxyphene could have contributed to the reported events based on its temporal (event onset of 2 days after ingestion) association. However, given the confounding factors of a previous history of cardiac related events, and the use of concomitant medications also labeled for cardiac associated events, the role of propoxyphene can not clearly established.

Representative Cases

ISR # 5185760 (Expedited Report, 2006)

A 48 year-old man presented with complaints of dizziness approximately 3 hours after taking his usual dose of metoprolol 100 mg and two tablets of propoxyphene 100/APAP 650. His blood pressure (BP) was 98/65 and the cardiac monitoring showed atrial fibrillation with ventricular response at 30-40 beats per minute. After treatment of the event (bradycardia), his heart rate (HR) increased to 50-70 beats per minute. At discharge (8 hours after presentation) his HR was 70 beats per minute. Serum drug profile concentrations obtained 30 minutes after presentation were metoprolol (160 ng/mL), diltiazem (99 ng/mL) and dextropropoxyphene (0.15 mcg/mL), which were within therapeutic levels[xxxiii]. Ten months later, this patient returned for a steady state metoprolol pharmacokinetic protocol. A peak metoprolol serum concentration of 89 ng/mL was observed at 3.5 hours. His HR significantly decreased with increasing metoprolol serum concentrations. This was reported as a case of profound bradycardia likely resulting from inhibition of metoprolol hepatic clearance by detropropoxyphene's effect on CYP 450 Enzyme System.

ISR #5483387 (Direct Report, 2007)

A 61-year-old female with a past medical history of an undetermined form of cardiomyopathy was found dead in her home. The circumstances at the scene were reported as typical for a sudden collapse due to a cardiac arrhythmia. Cardiomyopathy was the only reported past medical history. Postmortem analysis revealed a propoxyphene level of 2880 ng/mL (therapeutic range 200-800 ng/mL), Norpropoxyphene level of 6428 ng/mL (therapeutic range not established), duloxetine of 225 ng/mL (therapeutic range not established[xxxiv]). It was noted that duloxetine could have possibly increased the effects of propoxyphene, causing death due to arrhythmia; conversely, death could have been a

[xxxiii] Therapeutic levels for adults: metoprolol (beta-blocking activity)-35 to 212 ng/mL, diltiazem (antihypertensive activity)-40 to 200 ng/mL, propoxyphene-0.1 to 0.4 mcg/mL, nor-propoxyphene (metabolite)-0.1 to 0.15 mcg/mL.

[xxxiv] Oral administration of 20 and 30 mg duloxetine twice daily in healthy subjects, showed 15 ng/mL and 20 ng/mL respectively in one study (Sharma, et al, 2000).

complication of cardiomyopathy, independent of drug interaction effects. There were no other concomitant medications noted in the AERS report and no other drugs were detected during the postmortem analysis. Cardiac arrhythmias, ventricular fibrillation or cardiac arrest are labeled under symptoms of overdosage in the current labeling for propoxyphene containing products.

Psychiatric Related Event Cases (12)

There were 12 psychiatric related cases[xxxv] reported with use of a propoxyphene product: abnormal behavior-1, confusional state-3, hallucination-5, and mental status changes-6.

All 12 cases (12/12) reported using the propoxyphene combination product with acetaminophen (Darvocet). The onset of events related to treatment ranged from 2 doses to 14 days (n=7), with one case reporting a positive dechallenge (negative dechallenge-2, unknown-9). Six (6/12) cases reported a possible contributing medical history (i.e., thyroid disorder, decreased kidney function, senile dementia, drug sensitivity) or use of labeled concomitant medications (unknown-6). The concomitant medications labeled for psychiatric related events included sedatives, benzodiazepines, donepizil, fluoxetine, levetiracetam, gabapentin, opiods, and pregabalin. Propoxyphene products are labeled for hallucination. Eighty-three-percent of these cases (10/12, 83%), reported a contributing medical history or reported using concomitant medications labeled for CNS effects, however, a temporal association (n=7) and a positive dechallenge (n=1) suggest that propoxyphene products may be associated with the reported events in some cases. Further, the reduced metabolism in the elderly population and the pharmacodynamic[xxxvi] effects may also have contributed to these events.

Representative Cases

ISR #4889414 (Expedited, 2006)

A 68 year old patient became "nasty, agitated, mean, impatient, enraged, etc." after one week of treatment with a different "brand" of Darvocet-N 100. (She reported previous use of Darvocet for 7 years as needed for pain [dose not specified]). This event continued for 3 weeks and self-resolved. Diazepam[xxxvii] was the only concomitant medication reported (specific dose and duration of use not given). She believed the refilled Darvocet prescription was a generic or contained Nutrasweet. She had a similar experience with Nutrasweet in the past. Darvocet-N 100 was continued from two new prescriptions with no further problems. No other pertinent information was provided.

[xxxv] A case may have more than one reported preferred term

[xxxvi] Barkin R, et al. American Journal of Therapeutics 13, 538 (2006)

[xxxvii] Current diazepam labeling include hyperexcited states, hallucination, anxiety and rage.

ISR #5011076 (Direct, 2006)

A pharmacist reported that a 92-year-old female with a past medical history of hypertension, blindness, and temporal arteritis was admitted to the hospital for a 2-week history of altered mental status. The patient had begun taking Darvocet for back pain 2 weeks prior to admission and started having hallucinations, loss of appetite, and confusion. Her review of systems was otherwise negative. She stopped taking Darvocet three days prior to admission. The patient's altered mental status was attributed to Darvocet, and the patient was discharged to a nursing home. Concomitant medications were unknown and no follow-up information was provided.

ISR #5131914 (Expedited, 2006)

A 78 yr old female Alzheimer patient was admitted to the hospital due to a fall. Darvocet was prescribed during hospitalization for complaint of back pain. The patient's daughter observed in her mother the same sedative effects ("spacey") from Darvocet that her mother displayed while taking Percocet in the past. Ongoing concomitant medications were donepezil and fluoxetine[xxxviii]. No other pertinent medical history was reported. A week after hospitalization, the patient was transferred to a rehabilitation facility. A month later, Darvocet was discontinued and the reported event resolved.

Multiple Drug Overdose Cases (N=9)

Nine cases were reported as accidental drug overdose[xxxix]. Outcomes for these cases were death-8 and hospitalization-1. Almost all (8/9) cases reported using multiple drugs, and in two (2/8) cases alcohol was also involved. The most commonly reported suspect concomitant drugs were opioids[xl](n=8) or benzodiazepines (n=5). Only one case reported using a nonopiod concomitant drug (mirtazipine) in addition to propoxyphene. A history of drug abuse or addiction was reported in six (6/9) cases[xli]. In these six cases, outcome was attributed to ingestion of multiple drugs producing mixed drug toxicity and accidental death. In two of the three remaining cases, oxycodone was the primary suspect drug but the role of propoxyphene containing products could not be ruled out. In the remaining case, accidental death of a 30 year old female was attributed to propoxyphene, with mirtazipine reported as the contributory drug (see representative case below for details).

[xxxviii] Somnolence was a reported adverse event during the clinical trials for both donepezil and fluoxetine.

[xxxix] One case was reported as "narcotic overdose."

[xl] Oxydocone was most commonly reported suspect concomitant drug. Duragesic, morphine, methadone, hydromorphone, codeine, cocaine, and hydrocodone were also included as the suspect drugs.

[xli] Two (2/6) cases reported cocaine or ethanol abuse in addition to other drugs.

Representative Cases

ISR #5538276 (Expedited, 2007)

A 30-year-old female died after using single ingredient propoxyphene (Darvon) to treat back pain due to severe scoliosis and post-operative pain. Dose, frequency, and specific dates were unknown. According to the autopsy report, the patient died during sleep from an accidental over-ingestion of propoxyphene. Autopsy findings included pulmonary edema, cerebral edema, and diffuse visceral congestion. Therapeutic levels of mirtazapine were also reported as contributing to the events.

Drug Ineffective Cases (N=10)

All 10 cases reported the use of the propoxyphene/acetaminophen (Darvocet) combination product for pain (back, joint, leg, muscle, nerve)-6, pain (location not specified)-3, and osteoarthritis-1 [xlii]. Drug sensitivity or drug intolerance to aspirin, codeine, morphine, and Vicodin were reported as contributing past medical history in two (2/10) cases.

Six of the 10 cases reported the drug was ineffective or caused side effects (dizziness, nausea, vomiting) after switching from one brand (trade or generic brand) to a different generic product. Three cases suggested a lack of efficacy when used for an unlabeled indication (nerve pain)-1 and suboptimal potency at therapeutic doses-2. One case could not be assessed due to lack of information. The remaining six of the 10 cases reporting a product switch suggest a possible suboptimal potency associated with certain propoxyphene containing products (brands were not specified).

Elderly Population Cases (65 years or greater, N=26)

In forty percent (26/65, 40%) of the cases, patients were 65 years of age or older. Frequently reported adverse events in this age group were labeled events for the propoxyphene products (12/26, 46%) involving psychiatric (hallucination, confusion, mental status changes, abnormal behavior) or central nervous system (coma, ataxia) related events. There was no notable or consistent pattern of adverse events in the remaining 14 cases (14/26, 54%). The reported events varied widely and included cardiac related events (bradycardia, tachycardia)-3, liver function test elevated-2, drug ineffective-3, drug interaction[xliii]-1, and others (hypersensitivity, hip fracture, accidental drug overdose, and skin bruising, hepatomegaly)-5.

In one case, the use of warfarin with propoxyphene in a 79 year old male patient resulted in a significant increase in INR (14.1). The patient was treated with vitamin K and released from the hospital with an INR of 1.2. The only new medication recently added to the patient's regimen (phenytoin and warfarin) was propoxyphene. There was no pertinent contributing medical history. A drug interaction for propoxyphene with warfarin is a

[xlii] Duration of use prior to the reported event or switching to a different brand was reported in two (2/10) cases: 2.5 years and 16 years (unknown-8).

[xliii] The drug interaction involved warfarin and a single ingredient propoxyphene. Drug interaction with warfarin is a labeled event.

labeled event in the propoxyphene labeling[xliv]. Although a majority of these cases (20/26, 77%) reported underlying medical history or multiple co-suspect medications, propoxyphene containing products may have contributed to the events reported in the elderly population given the temporal association (10/26, 38%) and positive dechallenge (4/26, 15%) in some cases (most notably for psychiatric events).

There was one additional case of a plausible drug interaction involving carbamazepine in a female patient of unknown age. After two doses of Darvocet N 50 mg, the patient became unresponsive. She subsequently recovered after treatment with naloxone in the ER. Concomitant medications were carbamazepine 600 mg twice daily, Depakote EC 750 daily, and pregabalin 50 mg twice daily. Carbamazepine, depakote, and APAP levels were measured; carbamazepine levels were elevated at 19 mcg/mL[xlv]. After Darvocet and carbamazepine were held due to a suspected drug-drug interaction, the patient was much more alert and responsive the next morning. Carbamazepine level was now at13 mcg/mL. Drug interaction with carbamazepine is labeled in the current propoxyphene labeling.

Death Cases (N=12)

There were a total of 12 (12/65) fatal cases. Eleven (11/12) of these are described in previous sections (accidental overdose and cardiac) of the review. The cause of death in these 11 cases were reported as accidental overdose-8, cardiac-respiratory arrest-2, and arrhythmia-1. The remaining death case reported cerebral haemorrhage-1 as the cause. In this case, a 50-year-old male nursing home patient experienced a massive right hemispheric intracerebral hematoma with intraventricular hemorrhage. His medical history included hypertension, renal insufficiency, thrombus of left ventricle, congestive heart failure and cardiomyopathy. Rofecoxib (dose, duration, indication not reported) was reported as the primary suspect drug and the concomitant medications were atorvastatin, digoxin, warfarin, and Darvocet-N. After receiving meperidine and promethazine for joint pain, the patient became somnolent for a few hours and he was subsequently found unconscious with agonal respiration. The patient was given a CPR and intubated, then transferred to an ICU in a comatose state. The death certificate listed the cause of death as intracerebral hemorrhage.

3.2 LITERATURE REVIEW

3.2.1 Cardiac Effects of Therapeutic Doses of Propoxyphene

Two studies were identified comparing therapeutic dose propoxyphene to another drug or placebo (Appendix 1 Table 1). The first study by Salzman et al. compared propoxyphene hydrochloride to suprofen in a randomized parallel study. [1] Sixty-one percent of participants completed the study. Withdrawal rates were similar in both treatment groups and participants on propoxyphene withdrew due to non-cardiac side effects. No clinically significant changes in pulse or blood pressure were detected. Four participants had

[xliv] Refers to all current propoxyphene containing product labeling.

[xlv] Therapeutic levels of carbamazepine for seizure disorder: 4 to 12 mcg/mL

abnormal electrocardiograms (ECG) after the 24-week period. The authors concluded that the changes were not related to the study medications, though the reasons for their conclusion were not specified.

The study by Lang-Jensen et al. compared dextropropoxyphene napsylate to placebo in a younger patient sample.[2] In this case-crossover study design in which subjects served as their own controls, the completion rate was 90%. Only 10 young healthy males participated in the study and took propoxyphene or placebo three times daily for 16 days then switched to placebo or propoxyphene, respectively, after a one month washout period. The hemodynamic measurements taken at rest and during 30% and 60% work load showed a longer pre-ejection period in the propoxyphene group (mean =125ms) compared to the placebo group (mean =119). Overall hemodynamic measurements showed no effect on cardiac muscle contractility.

3.2.2 Cardiac Effects of Propoxyphene Overdose

We identified 14 publications describing cardiotoxic effects of propoxyphene when taken in overdose. All but one were case reports or case series (Appendix 1 Tables 2 & 3).

Afshari et al. 2005 conducted a two-part observational study, one included a prospective cohort design, and the other was a retrospective cohort without a comparison group. [3] The prospective study found an increase in QRS duration on ECG in the propoxyphene-paracetamol group (mean=99.36 milliseconds (ms); 95%CI = [96.19, 102.53]) compared to the group on other opioid-paracetamol combinations (mean = 82.84 ms; 95% C I= [80.81, 84.88]). None of the patients had abnormally prolonged QRS (> 0.12sec). In their retrospective study, they found a significant correlation between QRS duration and the plasma paracetamol concentration, which was used as an estimate of ingested propoxyphene dose (r = 0.338, p=0.003).

We identified 12 case reports describing a total of 14 cases. Four reports describe cases of propoxyphene overdose in older patients (aged 45 to 60 years) who experienced cardiac events.[4-7] Six patients had electrocardiograms showing widened QRS complexes (> 0.1sec). Respiratory depression preceded cardiac event in 3 of those patients, one patient had sudden cardio-respiratory failure, and the other 2 showed no signs of respiratory depression. First degree atrioventricular (AV) block was experienced by 5 patients.[5,8-11]

Sloth et al. described a case series of 222 patients with various cardiac events including bradycardia, tachycardia, and ventricular arrhythmias following propoxyphene overdose.[16]

3.3 DRUG USE DATA

3.3.1 Outpatient Dispensed Prescriptions

Table 1 in Appendix 3 shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for single-agent and combination propoxyphene products. There has been a slight decrease in the number of prescriptions dispensed for

propoxyphene products between years 2006 and 2007. During year 2007, approximately 22.3 million prescriptions were dispensed for all propoxyphene containing products with the majority of prescriptions being dispensed for propoxyphene/APAP (21.7 million dispensed prescriptions, 97.5%). The number of prescriptions dispensed for propoxyphene/asa/caffeine has decreased over the two years from nearly 6,800 prescriptions in year 2006 to approximately 400 prescriptions dispensed in year 2007.

3.3.2 Outpatient Dispensed Prescriptions by Age

Table 2 in Appendix 3 shows the total number of prescriptions dispensed by product and age in the outpatient retail setting for single-agent and combination propoxyphene products. For propoxyphene/APAP products, the majority of prescriptions dispensed were evenly split between adults age 45-64 years and elderly 65 years and greater with 38% in year 2007. While propoxyphene and propoxyphene/asa/caffeine were dispensed to adults age 45-64 years (48% and 42%, respectively) with a slightly greater frequency than elderly 65 years and greater (35% and 40%, respectively).

3.3.3 Patient Count

Trends for patient data were similar to that of prescription data, (Appendix 3: Table 3). For the entire study period, the majority of patients received propoxyphene/APAP products in the outpatient retail pharmacy setting. In year 2007, a total of 9.8 million patients received a prescription for a propoxyphene containing product. Of those, approximately 9.7 million (98.7%) patients were prescribed propoxyphene/APAP followed by propoxyphene with 182,000 (2%) patients.

3.3.4 Patient Count by Age

Table 4 in Appendix 3 shows the total number of patients receiving a prescription for single-agent and combination propoxyphene products by age. For propoxyphene/APAP products, the majority of patients receiving a prescription were evenly split among adults 18-44, 45-64, and 65 years and greater with approximately 3.1 million, 3.4 million, and 3.1 million, respectively. Patients aged 45-64 years receive a prescription for propoxyphene and propoxyphene/asa/caffeine with a slightly greater frequency than elderly 65 years and greater.

3.3.5 Prescriber Specialty

General Practice/Family Medicine/Doctor of Osteopathy was the most common prescribing specialty for all the products of single-agent and combination propoxyphene followed by Internal Medicine (Appendix 3: Table 5). During the most recent calendar year 2007, approximately 29% of the dispensed prescriptions were written by General Practice/Family Medicine/Doctor of Osteopathy for propoxyphene/APAP followed by 19% written by Internal Medicine physicians. In year 2007, 31% of dispensed prescriptions for propoxyphene and 38% of prescriptions for propoxyphene/asa/caffeine were written by General Practice/Family Medicine/Doctor of Osteopathy followed by Internal Medicine physicians with 23% and 13%, respectively.

4 DISCUSSION

4.1 UPDATED AERS CASES (N=65, 2006-2007)

The findings of this updated review were qualitatively similar to the findings in a prior OSE review completed in 2005[iv]. A direct causal role of propoxyphene products could not be established based on the underlying medical conditions and the use of multiple co-suspect medications in both the 2005 and the updated reviews.

Seventy-eight-percent of the cases (51/65) reported using the propoxyphene combination product containing acetaminophen[xlvi], 9% (6/65) reported using the single ingredient (propoxyphene), and an unknown formulation was used in 12% (8/65). A majority of the cases did not report the dose (52/65, 80%), time to onset of events (47/65, 72%), or duration of therapy (49/65, 75%). Of the 13 cases reporting a dose, most (12/13, 92%) reported using within the recommended daily dose (600 mg). Only one case (1/13) reported using a dose above the recommended daily dose (800 mg). The estimated time to adverse event onset was a median of one day (range 1 day to 4 years) in the 18 cases reporting this information. Sixty-five percent (42/65) reported using concomitant medications. Most frequently reported CNS associated concomitant drugs were opioids (e.g. oxycodone and duragesic), psychotropics[xlvii], and benzodiazepines. Contributing factors[xlviii] (medical history or labeled medications) were reported in almost half (29/65, 45%) of the cases and unknown in 55% (36/65) of the cases.

Psychiatric (12) and cardiac (11) related events were the most frequently reported events followed by drug ineffective (10), and multiple accidental drug overdose (9). The remaining 23 cases varied widely in terms of type of events reported and included some reports with no particular pattern or notable characteristics. In 18 of the 23 cases the primary suspect drugs included Forteo, varenicline, taxotere, Enbrel, Ketek, Vicodin, Medrol, Keflex, pregabalin, Vfend, acetaminophen, duragesic, tramadol, and trileptal. A propoxyphene product was one of several co-suspect or concomitant medications (taken as needed or as an on-going pain reliever) in many of these cases, therefore, its role could not be clearly assessed[xlix].

Selected events are discussed and summarized below:

<u>Cardiac Events</u>

In most (8/11, 73%) of the cardiac related cases, the propoxyphene product was one of multiple concomitant medications which made it difficult to assess a clear drug- to-event association. The reported events (bradycardia-2, cardiac arrhythmia-1) in the three

[xlvi] Drug strength was not specified (particularly the acetaminophen component) in a majority of the cases.

[xlvii] Psychotropics: antidepressants, sedatives, antipsychotics.

[xlviii] Contributing factors refers to an underlying medical condition, past medical history or use of labeled concomitant medications that could have contributed to the reported adverse events.

[xlix] There was one (1/23) case of a plausible drug interaction involving carbamazepine in a female patient of unknown age. Drug interaction with carbamazepine and propoxyphene is labeled in the current propoxyphene labeling.

remaining cases may be associated with the use of propoxyphene product. There was a temporal association in one case reporting bradycardia (contributing factors were history of cardiomyopathy and labeled concomitant medications). The remaining two cases also suggested propoxyphene could be associated with potentiating cardiac events through possible drug interactions.

Elderly Population

In patients who were 65 years of age or older, 40% (26/65) of the cases reported adverse events that are labeled events for the propoxyphene products; 46% of these 26 cases (12/26) involved psychiatric (hallucination, confusion, mental status changes, abnormal behavior) or central nervous system (coma, ataxia) related events. While a majority of these cases (20/26, 77%) reported an underlying medical history or multiple co-suspect medications, propoxyphene containing products may have contributed to the reported events given the temporal associations (10/26, 38%) and positive dechallenges (4/26, 15%).

Deaths

Most of the fatal (8/12, 67%) cases involved accidental overdose with use of multiple medications including alcohol (in 3 of 8 cases) thereby rendering an assessment of propoxyphene's role problematic. Concomitant drugs included opioids and benzodiazepines, which themselves can be implicated in accidental overdose. Nonetheless, an additive effect for propoxyphene can not be ruled out. The remaining four (4/12) cases reported the use of a propoxyphene product with one other medication (fiorinal, diphenhydramine, duloxetine, and mirtazipine). All four cases implicated an overdosage of propoxyphene products[ix].

4.2 LITERATURE REVIEW

The body of literature is populated with more anecdotal reports describing cardiotoxicity than with epidemiology studies, and these case reports have overshadowed those few epidemiology studies that make inferences based on analytic data. Case reports and case series do not provide a scientific basis to infer causal associations and are generally used for generation of hypotheses upon which epidemiological studies can be designed.

The cardiac safety profile of propoxyphene and its metabolite norpropoxyphene have been scarcely studied in humans. Researchers intending to conduct such studies are faced with a number of methodological issues, some of which are manifested in the 3 prospective studies included in this review. Cases of overdose in which propoxyphene has been implicated usually involve other drugs and substances of abuse. In some instances up to 75% of propoxyphene overdose cases involved the co-ingestion of alcohol and/or another drug. [17] In their study, Afshari et al. barely addressed this issue and failed to screen for and adjust for such potential confounders. Although Salzman et al. did randomize their patients to treatment groups the study sample included older patients who suffered from other medical ailments and were prescribed other medications for those conditions. This is

important especially since the authors attribute the observed ECG changes to factors (unspecified in the publication) other than the two study drugs.

Drug screens have confirmed multi-drug ingestions in overdose patients even when little clinical suspicion exists. [17] Propoxyphene ingestion was verified by drug screen in only 3 of the 14 case reports and in 2 of the cases at least one other drug was detected.[4,10,12] In all the other case reports, ingestion was verified either by the patient or by counts of missing pills.

Until recently the methods used to measure propoxyphene and norpropoxyphene levels in human body fluids were unreliable and produced high variations even in inter-laboratory values.[17] In practice measurement of propoxyphene levels is usually regarded as irrelevant primarily due to the fact that naloxone has been very effective in treatment and management of overdose patients and its success has not been dependent on the ingested dose of propoxyphene.[18] This lack of availability of drug concentration complicates efforts to study and interpret any dose-response relationship that may exist. In their study, Afshari et al. attempted to retrospectively estimate propoxyphene concentrations at certain time points during the patients' clinical course by using routinely measured plasma paracetamol concentrations and an estimated paracetamol half-life of 4 hours. The authors assumed the plasma concentration ratios of the propoxyphene and paracetamol would mirror the ratio of the two components found in the combination pills. However, they did not adjust for the difference in their elimination kinetics. Thus the correlation detected between paracetamol concentrations and QRS duration cannot be correctly assumed to hold true for propoxyphene based on this methodology. In addition, they did not use a comparison group and in essence cannot interpret a correlation as a causal association. In the Salzman et al. study and in 2 case reports[6,12] propoxyphene and/or norpropoxyphene levels were directly measured and that data was used to show when steady states of the drug were reached but not to evaluate dose-response associations.

The occurrence of respiratory depression in relation to the timing of cardiovascular abnormalities adds to the controversy of propoxyphene poisoning. Hypoxia due to a respiratory-depression effect of propoxyphene could produce cardiovascular changes including cardiac conduction abnormalities but this has been refuted by some in vitro and animal studies that conclude the two pathways are separate.[10,19-21] In the Salzman et al. and the Lang-Jensen et al. studies none of the participants were monitored for signs of respiratory depression, and Afshari et al. made no mention of respiratory compromise in their patients even though all of them had presented with overdose. With regards to propoxyphene products, a better comprehension of this complex cardio-respiratory relationship and a more lucid outcome definition would aid in designing studies that could control for the potential confounding effects of respiratory depression on cardiotoxicity.

5 OVERALL CONCLUSIONS

- Propoxyphene products may have had additive effects that contributed to cardiac events given the temporal association[l] (5/11, 45%) and positive dechallenge (3/11, 27%) in some cases.
- Propoxyphene products may have contributed to the psychiatric related events in some cases given temporal associations[li] (7/12, 58%) and a positive dechallenge (1/12).
- Over one-third (10/26, 38%) of the cases involving the elderly patients (65 years or older) reported psychiatric (e.g. hallucination, confusion, mental status changes) events which may reflect pharmacodynamic effects of propoxyphene in this population.
- Cases of plausible drug interactions in this review suggest that propoxyphene taken concomitantly with certain drugs[lii] may be associated with increased concentrations of propoxyphene or the co-administered drug, resulting in potentially life threatening toxicity (including cardiac events).
- The increased risk of fatalities from overdosage when propoxyphene products are used in combination with opioids, benzodiazepines, antidepressants, or other CNS depressants noted in this review is consistent with current product labeling. However, a direct causal role in fatalities for therapeutically administered propoxyphene could not be established given patients' underlying medical history, or use of multiple co-suspect drugs, or both, noted in a majority of reviewed cases.
- The findings in this updated review of propoxyphene product associated events are consistent with the 2005 OSE Postmarketing Review. The direct causal role of Darvocet in all 91 death cases in the prior OSE review could not be determined based on the underlying medical conditions or multiple co-suspect medications. In addition**, t**he top 20 event terms reported for serious U.S. cases (2006 to 2007) fairly represented the event terms reported for all U.S. cases reported from approval to 9/24/2008. The most reported terms were completed suicides, overdose (all types), and cardiac arrest.
- Despite current propoxyphene label warnings, narcotic pain relievers and other CNS related drugs continue to be prescribed and used with propoxyphene containing products, including in elderly patients.
- Literature review revealed mostly anecdotal reports of propoxyphene-related cardiotoxicity and lacked sound scientific evidence to support an association between propoxyphene-contanining products and cardiotoxicity.
- In 2007, the majority of sales of single-agent and combination propoxyphene products were to retail pharmacy settings. The propoxyphene/APAP product is the

[l] Five cases reported the estimated onset from 3 hrs to 21 days from starting the propoxyphene product.

[li] Estimated onset from day 1 of starting propoxyphene products: 2 doses to 14 days (n= 7)

[lii] Carbamazepine, duloxetine, metoprolol, and warfarin

most commonly dispensed to all the age groups, and is reflected in both the 2005 and this updated review.

- The trends for patient data (i.e., prescriptions received) were similar to prescription data (i.e., prescriptions filled) with respect to the propoxyphene formulations.
- General Practice/Family Medicine/Doctor of Osteopathy physicians are the most common prescribing healthcare providers for all propoxyphene containing products.

6 RECOMMENDATIONS

Although serious adverse events including death, many involving accidental and intentional overdosages with other, often multiple medications, continue to be reported with the use of propoxyphene containing products, the AERS data in this review are alone insufficient to substantially inform the question of phased withdrawal of propoxyphene containing drugs from the market requested by the Citizen's Petition. In OSE's opinion, the regulatory action recommended for FDA by the upcoming AC should be based on clear clinical evidence of propoxyphene efficacy satisfactory to inform a robust discussion of the risk/benefit profile for these drugs.

Should propoxyphene containing drugs remain on the market, we recommend consideration of additional regulatory action (e.g., strengthened labeling, or Risk Evaluation and Mitigation Strategies [REMS], or both) to address the ongoing concomitant use of these products with opioids, benzodiazepines, alcohol, and other problematic medications that continues despite current labeling precautions. Additionally, we recommend consideration of a post-marketing commitment for a clinical safety trial(s) should these products remain market approved.

7 REFERENCES

(1) Salzman RT, Brobyn RD. Long-term comparison of suprofen and propoxyphene in patients with osteoarthritis. *Pharmacology.* 1983;27 Suppl 1:55-64.

(2) Lang-Jensen T, Thisted B, Krantz T, Sorensen MB, Jacobsen E, Angelo HR. Cardiovascular function measured by ultrasound Doppler in healthy young men after ingestion of dextropropoxyphene napsylat. *Pharmacol Toxicol.* 1989;64:228-232.

(3) Afshari R, Maxwell S, Dawson A, Bateman DN. ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. *Clin Toxicol (Phila).* 2005;43:255-259.

(4) Sigurd BM, Jensen G. Propoxyphene poisoning. A case complicated by circulatory arrest caused by asystole followed by reversible heart pump failure. *Dan Med Bull.* 1971;18:166-168.

(5) Stork CM, Redd JT, Fine K, Hoffman RS. Propoxyphene-induced wide QRS complex dysrhythmia responsive to sodium bicarbonate--a case report. *J Toxicol Clin Toxicol.* 1995;33:179-183.

(6) Hantson P, Evenepoel M, Ziade D, Hassoun A, Mahieu P. Adverse cardiac manifestations following dextropropoxyphene overdose: can naloxone be helpful? *Ann Emerg Med.* 1995;25:263-266.

(7) Marraffa JM, Lang L, Ong G, Lehmann DF. Profound metoprolol-induced bradycardia precipitated by acetaminophen-propoxyphene. *Clin Pharmacol Ther.* 2006;79:282-286.

(8) QURESHI EH. PROPOXYPHENE HYDROCHLORIDE POISONING. *JAMA.* 1964;188:470-471.

(9) Barraclough CJ, Lowe RA. Failure of naloxone to reverse the cardiotoxocity of Distalgesic overdose. *Postgrad Med J.* 1982;58:667-668.

(10) Whitcomb DC, Gilliam FR 3rd, Starmer CF, Grant AO. Marked QRS complex abnormalities and sodium channel blockade by propoxyphene reversed with lidocaine. *J Clin Invest.* 1989;84:1629-1636.

(11) Staikowsky F, Candella S, Raphael M. Dextropropoxyphene and the cardiovascular system: about two cases of acute poisoning with cardiac conduction abnormalities. *J Opioid Manag.* 2005;1:240-243.

(12) Ogbuihi S, Bohn G, Audick W. Fatal case of propoxyphene overdose. Morphological and toxicological findings. *Z Rechtsmed.* 1980;84:161-166.

(13) Heaney RM. Left bundle branch block associated with propoxyphene hydrochloride poisoning. *Ann Emerg Med.* 1983;12:780-782.

(14) Starkey IR, Lawson AA. Acute poisoning with Distalgesic. *Br Med J.* 1978;2:1468.

(15) Marsden AK, Mora FM. Case report--the successful use of naloxone in an asystolic pre-hospital arrest. *Resuscitation.* 1996;32:109-110.

(16) Sloth Madsen P, Strom J, Reiz S, Bredgaard Sorensen M. Acute propoxyphene self-poisoning in 222 consecutive patients. *Acta Anaesthesiol Scand.* 1984;28:661-665.

(17) Buckley BM, Vale JA. Dextropropoxyphene poisoning: problems with interpretation of analytical data. *Hum Toxicol.* 1984;3 Suppl:95S-101S.

(18) Proudfoot AT. Clinical features and management of Distalgesic overdose. *Hum Toxicol.* 1984;3 Suppl:85S-94S.

(19) Ulens C, Daenens P, Tytgat J. Norpropoxyphene-induced cardiotoxicity is associated with changes in ion-selectivity and gating of HERG currents. *Cardiovasc Res.* 1999;44:568-578.

(20) Bredgaard Sorensen M, Strom J, Sloth Madsen P, Angelo HR, Reiz S. Haemodynamic, electrocardiographic and cardiometabolic changes after overdose of propoxyphene. An experimental study in pentobarbitone-anaesthetized pigs. *Hum Toxicol.* 1984;3 Suppl:53S-59S.

(21) Strom J. Acute propoxyphene self-poisoning--with special reference to propoxyphene cardiotoxicity and treatment. *Dan Med Bull.* 1989;36:316-3

APPENDIX 1:

TABLE 1. EPIDEMIOLOGICAL STUDIES: PROPOXYPHENE IN THERAPEUTIC DOSE

Reference	Population	Study Design	Exposure Variables	Outcome Measures	Key Findings
Salzman 1983[1]	Adults (mean age 60.25) with chronic pain & osteoarthritis n=114	Double-blind randomized controlled study	PPX 65mg versus Suprofen 200mg four times daily for 24 weeks	ECG changes measured at baseline and at 24 weeks	- 2 of 59 (3.4%) patients on suprofen and 2 of 55 (3.6%) patients on PPX had abnormal ECG changes not related to PPX - type of change not specified
Lang-Jensen 1989[2]	Healthy young male volunteers n=10	Double-blind randomized pre-post study	100mg DPX napsylate versus placebo t.i.d for 16 days	Cardiac output measures; HR, PEP, LVET, STI, STD, VHR, MAP	- Prolonged PEP in DPX group (125ms ± 11.34) compared to placebo (119ms ±11.34) at 60% of maximum work -No decrease cardiac contractility -No significant change at other work loads or in other measures

PPX=propoxyphene, DPX = Dextropropoxyphene, HR = heart rate, PEP= pre-ejection period, LVET = left ventricular ejection time, STI = systolic time interval, STD = stroke distance, VHR= maximum velocity of blood in ascending aorta X HR, MAP = mean arterial pressure

TABLE 2. EPIDEMIOLOGICAL STUDIES: PROPOXYPHENE IN OVERDOSE					
Reference	**Population**	**Study Design**	**Exposure Variables**	**Outcome Measures**	**Key Findings**
Afshari 2005[3]	Patients admitted with diagnosis of PPX overdose n=30	Prospective Cohort	PPX-paracetamol versus other opioid-paracetamol combo	ECG changes at 4hrs post-ingestion then q6-8 hr post-ingestion; QRS duration, PR interval, QTc interval	- Significant difference in QRS duration; PPX group mean duration = 99.36msec [95% CI = 96.19, 102.53] compared to Control group mean = 82.84msec [95% CI = 80.81, 84.88]
	Unspecified population n=74	Retrospective Cohort (no comparison group)	Plasma Paracetamol concentration as proxy for PPX dose	Cardiac indices; BP, HR, and QRS duration, PR interval and QTc interval on ECG	- Correlation between estimated paracetamol concentration and QRS duration (r=0.338, p=0.003)

PPX=propoxyphene, HR = heart rate, BP = blood pressure

TABLE 3. CASE REPORTS OF CARDIOTOXICITY	
Reference	**Case Findings**
Sigurd 1971[4]	• 45 year old male experienced sudden circulatory arrest with no preceding respiratory depression. • ECG initially revealed asystole, followed by widened QRS complexes with no identifiable P waves after treatment with 1mg adrenaline. • He remained hypotensive and without pulse until treatment with 5mg isoprenaline after which his ECG showed tachycardia with right axis deviation. • Propoxyphene and barbiturate discovered in urine and serum respectively
Stork 1995[5]	• 54 year old female ingested approximately 100 propoxyphene hydrochloride pills (6500mg) • Developed seizures followed by cardio-respiratory arrest. After resuscitation ECG showed wide QRS complexes with no identifiable P waves. ECG returned to normal sinus rhythm after receiving 200mEq sodium bicarbonate
Hantson	Case 1: 60 year old female with pre-end stage renal disease being treated for 1 year with

1995[6]	dextropropoxyphene-acetaminophen (515mg daily) for Paget's bone disease was admitted for shock and acute dyspnea. ECG changes: • Few weeks pre-admission – normal sinus rhythm with 1st degree AV block • Day 1 admission 1st ECG – 3rd degree SA block AV junction escape with left bundle branch block • Day 1 admission post-naloxone - sinus rhythm, prolonged PR interval .22 sec (1st degree AV block) • Day 2 admission – sinus rhythm, 1st degree AV block Case 2: 30 year old male admitted with 22.5gm overdose of dextropropoxyphene experienced decreased left ventricular stroke work index (18 gm/m^2; normal = 40 to 50 gm/m^2) which normalized after administration of naloxone, and ECG showed irregular sinus rhythm, tachycardia (110 beats/min).
Marraffa 2006[7]	• 48 year old male with long-standing atrial fibrillation on maintenance dose of 100mg metoprolol • Experiences profound bradycardia (30 beats/min) 4 hours after ingestion of metoprolol and first dose ever of propoxyphene napsylate 200mg/acetominophene 1300mg.
Qureshi 1964[8]	• 18 year old female suffered convulsions and respiratory depression following ingestion of 832 mg of propoxyphene hydrochloride. • ECG findings upon admission included sinus tachycardia and widened QRS complexes consistent with right bundle branch block.
Barraclough 1982[9]	• 18 year old male ingested 50 pills of propoxyphene 32.5mg/paracetamol 325mg following moderate intake of beer. • ECG revealed wide QRS complexes and right axis deviation. • No respiratory arrest or hypoxia was experienced throughout his hospital course.
Whitcomb 1989[10]	• 35 year old female's drug screen showed toxic levels of propoxyphene and traces of antidepressant • Presented with seizures, bradycardia, and progressively prolonged QRS duration

TABLE 3 CONTD. CASE REPORTS OF CARDIOTOXICITY	
Staikowsky 2005[11]	Case 1: 29 year old male former heroin addict ingested 1300mg dextropropoxyphene along with benzodiazepines and paracetamol. • ECG showed broad QRS complexes with, right bundle branch block, and absent P waves Case 2: 21 year old drug-addicted female ingested unknown amount of propoxyphene and benzodiazepine. • ECG revealed 1st degree AV block
Ogbuihi 1980[12]	• Autopsy on 21 year old female. • Histological evaluation of myocardium revealed signs suggestive of cardiotoxicity. • Body fluid analysis estimated ingestion of approximately 1500mg propoxyphene hydrochloride about 2.5 hours prior to death. • No other medications detected.
Heaney 1983[13]	• 20 year old male with a history of recreational drug use and seizure disorder for which he took phenytoin 100mg three times a day. • Developed Grade I/II systolic murmur with splitting of S1 and S2, and left bundle

	branch block with 1st degree AV block after taking an overdose of 1105mg of propoxyphene hydrochloride. • The cardiac signs resolved after 8 hours of admission during which he received 3 doses of naloxone 0.4 mg IV and intravenous saline infusion.
Starkey 1978[14]	• 15 year old female suspected of taking 50 pills of propoxyphene 32.5mg/paracetamol 325mg • ECG showed asystole which changed to 1st degree heart block, complete right bundle branch block and extreme axis deviation after resuscitation.
Marsden 1996[15]	• 30 year old female ingested 80 tablets of dextropropoxyphene 32.5mg/paracetamol 325mg. • Suffered convulsions and cardio-respiratory arrest • Returned to sinus tachycardia after administration of 2 doses of 0.4mg naloxone IV. • Declared brain dead due to cerebral anoxia 24 hours later.
Sloth 1984[16]	222 consecutive cases of propoxyphene poisoning. • Impaired circulation in 48% • Bradycardia in 9% • Tachycardia in 15% • ECG abnormalities in 41% (43 patients with widened QRS complexes, 1 with 1st degree AV Block, 19 with ventricular arrhythmias

APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription

claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

APPENDIX 3: TABLES

Table 1: Total Number of Dispensed Prescriptions of Single Agent and Combination Propoxyphene by Product Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	Retail TRxs N	*Share %*	Retail TRxs N	*Share %*
TOTAL MARKET	**23,098,536**	***100.0%***	**22,327,677**	***100.0%***
Propoxyphene/APAP	22,519,909	*97.5%*	21,770,334	*97.5%*
Propoxyphene-N/APAP	21,939,637	*97.4%*	21,329,727	*98.0%*
Darvocet-N 100	290,994	*1.3%*	235,424	*1.1%*
Propoxyphene w/APAP	173,719	*0.8%*	144,915	*0.7%*
Balacet 325	86,864	*0.4%*	47,639	*0.2%*
Darvocet A500	21,479	*0.1%*	8,707	*0.0%*
Darvocet-N 50	7,139	*0.0%*	3,820	*0.0%*
Propacet 100	43	*0.0%*	57	*0.0%*
Wygesic	20	*0.0%*	36	*0.0%*
Trycet	14	*0.0%*	9	*0.0%*
Propoxyphene	571,850	*2.5%*	556,926	*2.5%*
Propoxyphene	502,189	*87.8%*	491,316	*88.2%*
Darvon N	56,426	*9.9%*	55,154	*9.9%*
Darvon	13,235	*2.3%*	10,456	*1.9%*
propoxyphene/asa/caffein	6,777	*0.0%*	417	*0.0%*
Darvon Compound-65	6,560	*96.8%*	322	*77.2%*
Propoxyphene Cpd	217	*3.2%*	94	*22.5%*
Darvon Compound-32	--	--	1	*0.2%*

Source: SDI Vector One: National®. 2006-2007. Extracted 10/30/08. File: VONA 2008-1517 TRx Propoxyphene by Product.xls

Table 2: Total Number of Dispensed Prescriptions of Single Agent and Combination Propxyphene by Product and Age Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	Retail TRxs N	*Share %*	Retail TRxs N	*Share %*
TOTAL MARKET	**23,098,494**	***100.0%***	**22,327,745**	***100.0%***
Propoxyphene/APAP	22,519,867	*97.5%*	21,770,366	*97.5%*
Age 0-17	253,784	*1.1%*	235,895	*1.1%*
Age 18-44	5,305,875	*23.6%*	4,991,036	*22.9%*
Age 45-64	8,424,509	*37.4%*	8,181,307	*37.6%*
Age 65+	8,444,650	*37.5%*	8,297,000	*38.1%*
Age UNSPEC.	91,049	*0.4%*	65,128	*0.3%*
Propoxyphene	571,852	*2.5%*	556,956	*2.5%*
Age 0-17	2,701	*0.5%*	2,166	*0.4%*
Age 18-44	91,040	*15.9%*	86,508	*15.5%*
Age 45-64	278,111	*48.6%*	269,564	*48.4%*
Age 65+	197,263	*34.5%*	196,041	*35.2%*
Age UNSPEC.	2,737	*0.5%*	2,677	*0.5%*
propoxyphene/asa/caffein	6,775	*0.0%*	423	*0.0%*
Age 0-17	28	*0.4%*	1	*0.2%*
Age 18-44	552	*8.1%*	72	*17.0%*
Age 45-64	2,763	*40.8%*	179	*42.3%*
Age 65+	3,394	*50.1%*	167	*39.5%*
Age UNSPEC.	38	*0.6%*	4	*0.9%*

Source: SDI Vector One: National®. 2006-2007. Extracted 10/30/08. File: VONA 2008-1517 TRx Propoxyphene by Age.xls

Table 3: Total Number of Unique Patients Receiving a Prescription of Single Agent and Combination Propxyphene by Product Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	N	%	N	%
Grand Total	**10,211,876**	***100.00%***	**9,805,215**	***100.00%***
Propoxyphene/APAP	10,071,502	*98.63%*	9,671,368	*98.63%*
Propoxyphene-N/APAP	9,893,598	*98.23%*	9,546,166	*98.71%*
Darvocet-N 100	103,590	*1.03%*	81,063	*0.84%*
Propoxyphene w/APAP	73,937	*0.73%*	60,524	*0.63%*
Balacet 325	46,017	*0.46%*	21,983	*0.23%*
Darvocet A500	11,468	*0.11%*	4,143	*0.04%*
Darvocet-N 50	4,543	*0.05%*	2,422	*0.03%*
Propacet 100	31	*0.00%*	45	*0.00%*
Wygesic	16	*0.00%*	19	*0.00%*
Trycet	12	*0.00%*	9	*0.00%*
Propoxyphene	190,663	*1.87%*	182,312	*1.86%*
Propoxyphene	168,017	*88.12%*	160,961	*88.29%*
Darvon N	22,201	*11.64%*	21,319	*11.69%*
Darvon	3,276	*1.72%*	2,349	*1.29%*
propoxyphene/asa/caffein	4,487	*0.04%*	367	*0.00%*
Darvon Compound-65	4,330	*96.50%*	282	*76.78%*
Propoxyphene Cpd	163	*3.63%*	86	*23.42%*
Darvon Compound-32				

Source: SDI Vector One: Total Patient Tracker®. 2006-2007. Extracted 11/7/08. File: TPT 2008-1517 Propoxyphene Patient Count by Product.xls, TPT 2008-1517 Propoxyphene Asa Caff Patient Count.xls, TPT 2008-1517 Propoxyphene APAP Patient Count.xls

Table 4: Total Number of Unique Patients Receiving a Prescription of Single Agent and Combination Propxyphene by Age Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	N	%	N	%
Grand Total	**10,211,876**	***100.00%***	**9,805,215**	***100.00%***
Age 0-17	**223,418**	***2.19%***	**205,626**	***2.10%***
Propoxyphene/APAP	221,696	*99.23%*	204,269	*99.34%*
Propoxyphene-N/APAP	218,522	*98.57%*	202,405	*99.09%*
Darvocet-N 100	643	*0.29%*	473	*0.23%*
Propoxyphene w/APAP	1,581	*0.71%*	1,185	*0.58%*
Balacet 325	921	*0.42%*	310	*0.15%*
Darvocet A500	213	*0.10%*	55	*0.03%*
Darvocet-N 50	173	*0.08%*	74	*0.04%*
Propacet 100	-	-	-	-
Wygesic	-	-	-	-
Trycet	-	-	-	-
Propoxyphene	1,894	*0.85%*	1,550	*0.75%*
Propoxyphene	1,686	*89.01%*	1,372	*88.52%*
Darvon N	205	*10.85%*	184	*11.88%*
Darvon	8	*0.42%*	-	-
propoxyphene/asa/caffein	24	*0.01%*	1	*0.00%*
Darvon Compound-65	24	*100.00%*	1	*100.00%*
Propoxyphene Cpd	-	-	-	-
Darvon Compound-32	-	-	-	-
Age 18-44	**3,276,893**	***32.09%***	**3,091,950**	***31.53%***
Propoxyphene/APAP	3,247,528	*99.10%*	3,063,975	*99.10%*
Propoxyphene-N/APAP	3,198,792	*98.50%*	3,033,136	*98.99%*
Darvocet-N 100	17,322	*0.53%*	12,359	*0.40%*
Propoxyphene w/APAP	24,740	*0.76%*	19,175	*0.63%*
Balacet 325	16,798	*0.52%*	7,392	*0.24%*
Darvocet A500	3,248	*0.10%*	911	*0.03%*
Darvocet-N 50	919	*0.03%*	383	*0.01%*
Propacet 100	12	*0.00%*	12	*0.00%*
Wygesic	3	*0.00%*	5	*0.00%*
Trycet	1	*0.00%*	-	-
Propoxyphene	40,253	*1.23%*	38,411	*1.24%*
Propoxyphene	35,501	*88.19%*	33,929	*88.33%*
Darvon N	4,949	*12.29%*	4,726	*12.30%*
Darvon	287	*0.71%*	186	*0.48%*
propoxyphene/asa/caffein	419	*0.01%*	64	*0.00%*
Darvon Compound-65	401	*95.76%*	54	*84.06%*
Propoxyphene Cpd	18	*4.34%*	10	*16.12%*
Darvon Compound-32	-	-	-	-
Age 45-64	**3,563,162**	***34.89%***	**3,454,618**	***35.23%***
Propoxyphene/APAP	3,505,121	*98.37%*	3,398,308	*98.37%*
Propoxyphene-N/APAP	3,439,277	*98.12%*	3,351,685	*98.63%*
Darvocet-N 100	42,134	*1.20%*	33,342	*0.98%*
Propoxyphene w/APAP	25,162	*0.72%*	20,322	*0.60%*
Balacet 325	17,762	*0.51%*	8,971	*0.26%*
Darvocet A500	4,521	*0.13%*	1,815	*0.05%*
Darvocet-N 50	1,203	*0.03%*	803	*0.02%*
Propacet 100	13	*0.00%*	10	*0.00%*
Wygesic	8	*0.00%*	7	*0.00%*
Trycet	5	*0.00%*	7	*0.00%*
Propoxyphene	79,907	*2.24%*	77,037	*2.27%*
Propoxyphene	69,609	*87.11%*	67,107	*87.11%*
Darvon N	10,358	*12.96%*	10,072	*13.07%*
Darvon	1,442	*1.80%*	1,021	*1.33%*
propoxyphene/asa/caffein	1,794	*0.05%*	152	*0.00%*
Darvon Compound-65	1,728	*96.33%*	118	*77.63%*
Propoxyphene Cpd	71	*3.93%*	34	*22.10%*
Darvon Compound-32	-	-	-	-
Age 65+	**3,176,443**	***31.11%***	**3,109,387**	***31.71%***
Propoxyphene/APAP	3,124,551	*98.37%*	3,060,634	*98.43%*
Propoxyphene-N/APAP	3,063,170	*98.04%*	3,013,767	*98.47%*
Darvocet-N 100	43,566	*1.39%*	34,941	*1.14%*
Propoxyphene w/APAP	22,755	*0.73%*	20,006	*0.65%*
Balacet 325	10,472	*0.34%*	5,340	*0.17%*
Darvocet A500	3,465	*0.11%*	1,337	*0.04%*
Darvocet-N 50	2,190	*0.07%*	1,137	*0.04%*
Propacet 100	6	*0.00%*	19	*0.00%*
Wygesic	5	*0.00%*	3	*0.00%*
Trycet	7	*0.00%*	2	*0.00%*
Propoxyphene	68,199	*2.15%*	65,132	*2.09%*
Propoxyphene	60,819	*89.18%*	58,301	*89.51%*
Darvon N	6,687	*9.81%*	6,358	*9.76%*
Darvon	1,526	*2.24%*	1,160	*1.78%*
propoxyphene/asa/caffein	2,224	*0.07%*	145	*0.00%*
Darvon Compound-65	2,155	*96.88%*	104	*71.73%*
Propoxyphene Cpd	68	*3.05%*	43	*29.90%*
Darvon Compound-32	-	-	-	-
Age Unspec.	**146,180**	***1.43%***	**133,185**	***1.36%***
Propoxyphene/APAP	142,745	*97.65%*	129,826	*97.48%*
Propoxyphene-N/APAP	139,673	*97.85%*	127,305	*98.06%*
Darvocet-N 100	1,794	*1.26%*	1,584	*1.22%*
Propoxyphene w/APAP	1,021	*0.72%*	884	*0.68%*
Balacet 325	416	*0.29%*	199	*0.15%*
Darvocet A500	103	*0.07%*	104	*0.08%*
Darvocet-N 50	79	*0.06%*	35	*0.03%*
Propacet 100	2	*0.00%*	-	-
Wygesic	-	-	-	-
Trycet	-	-	-	-
Propoxyphene	3,685	*2.52%*	3,602	*2.70%*
Propoxyphene	3,327	*90.28%*	3,344	*92.83%*
Darvon N	268	*7.28%*	227	*6.30%*
Darvon	98	*2.66%*	39	*1.08%*
propoxyphene/asa/caffein	44	*0.03%*	4	*0.00%*
Darvon Compound-65	38	*86.04%*	4	*100.00%*
Propoxyphene Cpd	6	*13.96%*	-	-
Darvon Compound-32	-	-	-	-

Source: SDI Vector One: Total Patient Tracker®. 2006-2007. Extracted 11/7/08. File: TPT 2008-1517 Propoxyphene Patient Count by Age.xls, TPT 2008-1517 Propoxyphene by Age.xls, TPT 2008-1517 Propoxyphene APAP by Age.xls, TPT 2008-1517 Propoxyphene Asa Caff by Age.xls

Table 5: Total Number of Dispensed Prescriptions of Single Agent and Combination Propxyphene by Prescriber Specialty Through U.S Outpatient Retail Pharmacies, 2006-2007

	2006		2007	
	Retail TRxs N	*Share %*	Retail TRxs N	*Share %*
TOTAL MARKET	**23,098,560**	***100.0%***	**22,327,678**	***100.0%***
Propoxyphene/APAP	22,519,915	*97.5%*	21,770,322	*97.5%*
GP/FM/DO	6,506,989	*28.9%*	6,301,219	*28.9%*
IM	4,389,773	*19.5%*	4,184,684	*19.2%*
ORTH SURG	2,003,009	*8.9%*	1,928,175	*8.9%*
DENT	1,292,109	*5.7%*	1,271,342	*5.8%*
UNSPEC	815,191	*3.6%*	773,767	*3.6%*
OB/GYN	807,053	*3.6%*	771,653	*3.5%*
EM	765,853	*3.4%*	726,439	*3.3%*
GEN SURG	734,209	*3.3%*	672,319	*3.1%*
RHEUM	537,440	*2.4%*	525,652	*2.4%*
AO SURG	539,924	*2.4%*	516,475	*2.4%*
All Others	4,128,365	*18.3%*	4,098,597	*18.8%*
Propoxyphene	571,872	*2.5%*	556,937	*2.5%*
GP/FM/DO	180,220	*31.5%*	174,306	*31.3%*
IM	135,610	*23.7%*	129,834	*23.3%*
ORTH SURG	32,976	*5.8%*	30,841	*5.5%*
UNSPEC	24,508	*4.3%*	22,808	*4.1%*
RHEUM	22,002	*3.8%*	22,199	*4.0%*
NP	13,677	*2.4%*	15,220	*2.7%*
PA	12,107	*2.1%*	13,410	*2.4%*
PM&R	12,085	*2.1%*	13,066	*2.3%*
ANES	11,139	*1.9%*	11,504	*2.1%*
NEURO	12,048	*2.1%*	11,422	*2.1%*
All Others	115,500	*20.2%*	112,327	*20.2%*
propoxyphene/asa/caffein	6,773	*0.0%*	419	*0.0%*
GP/FM/DO	2,603	*38.4%*	159	*37.9%*
IM	1,760	*26.0%*	54	*12.9%*
ORTH SURG	275	*4.1%*	40	*9.5%*
DENT	202	*3.0%*	20	*4.8%*
UNSPEC	277	*4.1%*	18	*4.3%*
NP	99	*1.5%*	18	*4.3%*
GEN SURG	72	*1.1%*	17	*4.1%*
OB/GYN	235	*3.5%*	17	*4.1%*
EM	98	*1.4%*	9	*2.1%*
PM&R	41	*0.6%*	8	*1.9%*
All Others	1,111	*16.4%*	59	*14.1%*

Source: SDI Vector One: National®. 2006-2007. Extracted 10/30/08. File: VONA 2008-1517 TRx Propoxyphene by Prescribing Specialty.xls