

# History and Overview of the Safety and Efficacy of Propoxyphene Products

Presented at the  
Joint Meeting of the  
Anesthetic and Life Support Drugs Advisory Committee  
and  
Drug Safety and Risk Management Committee

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Xanodyne Pharmaceuticals, Inc.

# Overview

- Pain and Pain Management
- Citizen Petition
- Product History
- Safety and Efficacy of Propoxyphene Products
- Additional Topics
  - European experience
  - Abuse liability
  - DAWN data
  - Use in elderly
  - Cardiotoxicity

# Pain and Pain Management

- Epidemiology of Pain
  - Pain is diverse, debilitating, prevalent, undertreated
    - 25 million Americans annually experience acute, short-term pain caused by injury or surgery<sup>1</sup>
    - 48 million Americans (24%) experience chronic pain<sup>2</sup>
      - 40% cannot work
      - 60% cannot engage in daily activities
  - Annual cost of pain in the US is estimated to be \$100 billion, including healthcare expenses, compensation for lost work, and litigation<sup>3</sup>

1. American Academy of Pain Management, *Pain Issues: Pain is an Epidemic*.
2. National Pain Survey.
3. BA Coda & JJ Bonica, *General Considerations of Acute Pain*.

# Pain and Pain Management Options

- Varying etiologies, types of pain, and differences among patients make pain management challenging
  - Pain management requires multiple treatment options for different patient populations
  - Individual patients often require a multi-modal approach to manage pain
- Pain management requires availability of wide range of products
  - Treatment algorithm may range from simple analgesics to major opioids
  - Shrinking toolbox for pain management problematic

# Citizen Petition

# Citizen Petition

- Public Citizen has filed two Citizen Petitions requesting withdrawal of propoxyphene-containing pain management drugs from the market
  - Petitioned Department of Health Education and Welfare (HEW) in 1978
    - Petition denied in 1979
  - Petitioned Food and Drug Administration (FDA) on February 28, 2006 (Docket No. 2006P-0090)
    - Currently pending
    - Offers little more support than the 1978 Petition
      - DAWN data, UK experience

# Petitions' Arguments & Responses

- Argument:
  - Many of the deaths attributed to propoxyphene are due to “cardiotoxic” effect of major metabolite, norpropoxyphene
- Response:
  - 1978: HEW concluded there was little evidence that metabolite’s effects were a common factor in propoxyphene-associated deaths
  - 2006: Public Citizen provided little new data

# Petitions' Arguments & Responses

- Argument:
  - Propoxyphene can cause death or severe cardiac events *even when taken as directed*
- Response:
  - 1979: FDA concluded there were no well documented examples of death when drug taken according to labeling
  - HEW determined there was no clear evidence that propoxyphene can cause death when taken in accordance with labeling (i.e. in the absence of tranquilizers or alcohol)
  - HEW stated that identified deaths appeared to be the result of drug misuse

# Petitions' Arguments & Responses

- Argument:
  - Other analgesics are better alternatives to propoxyphene (including acetaminophen and aspirin)
- Response
  - 1979: FDA noted acetaminophen and aspirin are toxic at high doses and may not be safe options for some patients
  - NSAIDs have been the subject of significant risk concerns over the past several years, thus pain management options have been further reduced
  - Clinical studies indicate propoxyphene/acetaminophen combinations are superior to acetaminophen alone

# Product History

# General Propoxyphene History

- Long history of safe use in the U.S. and abroad, including South America, Europe, Africa, Australia, and Asia
- One of most widely prescribed treatments for mild to moderate pain
  - Over 23.3 million prescriptions filled in 2007<sup>1</sup>
  - One of the 40 most commonly prescribed drugs<sup>2</sup>
  - Age distribution of propoxyphene prescriptions<sup>2</sup>
    - Under 35: 20%
    - 35-44: 17%
    - 45-54: 18%
    - 55-64: 15%
    - 65 and older: 30%

1. IMS NPA (National Prescription Audit) for 12 months ending November 2008, January 2009.

2. SDI/Verispan's VONA (Vector One National Accounts) for the 12 months ending November 2008, January 2009.

3. SDI/Verispan PDDA (Physician Drug and Diagnosis Audit), January 2009.

# History: Propoxyphene-containing Drug Approvals

- Darvon approved based on safety in the 1950s
- Later approved for efficacy pursuant to Kefauver-Harris Drug Amendments of 1962 in the NAS/NRC DESI
- Subsequent approvals for new propoxyphene-containing drugs for new formulations (napsylate and hydrochloride), strengths, and combinations with other active ingredients (acetaminophen)
  - Darvocet A500 approved in 2003
  - 97 SKUs for propoxyphene-containing products with some sales in the past 24 months<sup>1</sup>
  - Most recent approval less than 1 year ago

1. IMS NSP (National Sales Perspective) for 12 months ending November 2008, January 2009.

# Data on Safety and Efficacy of Propoxyphene Products

# Methodological Issues in Determining Efficacy of Pain Medications

- Clinical evaluation of analgesics is complex
  - Difficult for patients to distinguish among analgesics
  - High placebo effect: 30% of individuals may obtain temporary relief of mild pain with placebo
  - Analgesic products have differing potencies and are difficult to compare
  - Changing standards in pain modeling (third molar extractions to bunionectomies)

# Initial Clinical Studies

- Supported approval of product for general use
- Multiple-dose assays demonstrated a dose-response relationship when given in doses of 0, 32.5 mg, and 64 mg every 4-6 hours
  - Gruber et al: The Effectiveness of d-Propoxyphene Hydrochloride and Codeine Phosphate as Determined by Two Methods of Clinical Testing for Relief of Chronic Pain (1956)
  - Gruber: Codeine Phosphate, Propoxyphene Hydrochloride, and Placebo (1957)
- Summary of results: Study drugs produced similar analgesic effect on each of 3 days of administration; pain scores were higher with placebo

# Summary of 7 Acute Pain Studies: Darvocet and Darvocet-N

- 7 randomized controlled clinical trials on efficacy of Darvocet were conducted with the same study design, by 3 different investigators, for post-partum pain secondary to uterine cramping or episiotomy
- Measurements of pain were made before administration and hourly for 8 hours after administration:
  - Pain intensity on a 0 to 4 scale
  - Relief on a 0 to 4 scale

Source: E.8. Overall Conclusions: Statistical Summary of the Darvocet and Darvocet-N Acute Pain Studies.

# Summary of 7 Acute Pain Studies: Darvocet and Darvocet-N

- From these data, the following were assessed:
  - Time to onset of analgesia
  - Total analgesic response over 6 hour period
  - Peak pain relief
  - Consistencies in medication with initial pain intensity
  - Consistencies or patterns in analgesic response with pain intensity
- Adjusted means for each active medication were compared to placebo using Dunnett's test

Source: E.8. Overall Conclusions: Statistical Summary of the Darvocet and Darvocet-N Acute Pain Studies.

## Summary of Results: 7 Acute Pain Studies

Studies consistently demonstrated greater analgesic effect of combination than either component alone

- Darvon (propoxyphene):
  - Darvon and acetaminophen alone were both better than placebo for analgesia at 1 or 2 hours and peak analgesia
  - No evidence of interaction of propoxyphene with acetaminophen; additive effect seen

Source: E.8. Overall Conclusions: Statistical Summary of the Darvocet and Darvocet-N Acute Pain Studies.

## Summary of Results: 7 Acute Pain Studies

Studies consistently demonstrated greater analgesic effect of combination than either component alone

- Darvocet (propoxyphene/acetaminophen):
  - Significantly more effective than placebo in 5 of 7 studies at either 1 or 2 hours and observationally (but not statistically) better in remaining 2 studies
  - Better than Darvon, acetaminophen, and placebo in total pain relief and peak analgesia

Source: E.8. Overall Conclusions: Statistical Summary of the Darvocet and Darvocet-N Acute Pain Studies.

# Evaluation of 50 Publications Comparing Propoxyphene Medications to Other Analgesics

- 50 studies published between 1956-1971 compared Darvon to codeine and its combinations, aspirin products, or placebo
  - Studies could not be grouped for a statistical analysis according to dose, causes and severity of pain, experimental design, or degrees of control

Source: Submission of Eli Lilly to the FDA, Re: Recommendations for Dextropropoxyphene under the Controlled Substances Act – Clinical Efficacy (dated Sept. 1973).

# Results of 50 Publications Comparing Propoxyphene Medications to Other Analgesics

- Trends indicated:
  - Darvon and its combinations were effective analgesics
  - Combination products appear superior to single-entities
  - Active medications were superior to placebo
  - Analgesic effect of Darvon combinations was greater in all 24 studies that compared Darvon combinations with placebo
  - Patients reported more side effects with codeine and its combinations than with Darvon and its combinations

Source: Submission of Eli Lilly to the FDA, Re: Recommendations for Dextropropoxyphene under the Controlled Substances Act – Clinical Efficacy (dated Sept. 1973).

# Comparison of Propoxyphene Salts

- Randomized double-blind trial of propoxyphene HCl (65 mg) vs. propoxyphene napsylate (100 mg) (n=316)
- Purpose: To obtain standardized efficacy ratings on drugs and safety information
- Ratings based on 4-point categorical scale (good, fair, poor, or don't know)

Jick et al. Randomized double-blind trial of propoxyphene HCl (65 mg) vs. propoxyphene napsylate (100 mg) in 316 patients. *Clin Pharmacol Ther*, 12(3):456 (1971).

# Results: Comparison of Propoxyphene Salts

- Patient and physician ratings agreed in 90% of cases
- Frequency of “good” and “fair” ratings was 75% in napsylate group and 79% in hydrochloride group ( $p=0.58$ )
- Discontinuation (secondary measure of efficacy): 10% for both groups
- Authors concluded: Salts were not distinguishable for efficacy; adverse events may be less frequent with napsylate salt, but side effects of both drugs were infrequent and minor

Jick et al. Randomized double-blind trial of propoxyphene HCl (65 mg) vs. propoxyphene napsylate (100 mg) in 316 patients. Clin Pharmacol Ther, 12(3):456 (1971).

# Propoxyphene + APAP Versus APAP Alone

- 4 clinical studies known to us testing the combination Propoxyphene/APAP versus APAP alone with a comparable dose of APAP (650 mg)
- Summary: Propoxyphene adds efficacy to APAP

1 <sup>st</sup> Author	Pain type	Sum of difference in pain intensity		
		APAP/Propoxyphene	APAP	Plbo
Cooper (1981)	Molar extraction	3.6	2.8	0.1
Hopkinson (1973)	Episiotomy	5.4	4.4	3.1
Liashek (1987)	Molar extraction	3.1	-0.5	-
Messick (1979)	Musculoskeletal	NR*	NR*	NR*

\*Not reported: However, study compared Plbo, APAP, APAP + Propoxyphene Napsylate, and APAP + Propoxyphene HCl. Combination products were statistically superior to Plbo while APAP alone was not.

# Veterans Affairs (VA) 2006 Review of Efficacy and Safety of Propoxyphene

- Update to VA's review of August 2001
- Considered new data on single-dose efficacy of propoxyphene, safety concerns associated with abuse of propoxyphene, and accidental fatal overdoses
- Evaluated evidence addressing the following:
  - In VA patients with acute or chronic pain, does the potential analgesic efficacy of propoxyphene alone or in combination exceed the potential risks of its adverse effects?
  - Cost effectiveness relative to other opioids?
  - Which agents may be used as therapeutic alternatives?

Source: VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, *Review of the Efficacy and Safety of Propoxyphene* (March 2006).

# Veterans Affairs 2006 Review Conclusions

- No substantive evidence found to alter previous conclusions about safety and efficacy relative to other opioids
- Recommendations on use of propoxyphene in the VHA remained essentially unchanged:
  - In majority of VA patients, with mild to moderate acute pain, who are not at risk for intentional or unintentional overdose, propoxyphene with or without APAP likely to provide adequate analgesia with acceptable safety for single-dose or short-term therapy

Source: VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, *Review of the Efficacy and Safety of Propoxyphene* (March 2006).

# Additional Topics

# Further Topics To Be Addressed

- European Experience
- Abuse liability
- Use in elderly
- Cardiotoxicity
- DAWN data

# UK Propoxyphene Experience

- January 2005: UK ordered phased withdrawal of co-proxamol from the market
  - Benefits did not outweigh risks
  - 300-400 self-poisoning deaths annually
- December 31, 2007: Market authorization cancelled
  - Drug available only on a named-patient basis
    - Prescribed as unlicensed product under direct physician responsibility
    - Physicians may still prescribe co-proxamol to patients who are likely to find it very difficult to change from co-proxamol or for whom alternatives appear to be ineffective or unsuitable
- UK import notification system for unlicensed drugs reported importation surge in 4th quarter, 2007

# UK Experience Not Comparable to US

UK	US
32.5 mg with 325 mg acetaminophen	50 - 100 mg with and without acetaminophen
<ul style="list-style-type: none"> <li>• Sold without prescription before 2005</li> <li>• Now available only on a named-patient basis</li> </ul>	<ul style="list-style-type: none"> <li>• Always prescription only</li> <li>• Schedule IV controlled substance since 1977</li> </ul>
Common suicide drug	Uncommon suicide drug
Taken as propoxyphene hydrochloride <ul style="list-style-type: none"> <li>• More soluble</li> <li>• Faster absorption</li> </ul>	96% taken as propoxyphene napsylate <ul style="list-style-type: none"> <li>• Less soluble</li> <li>• Slower absorption</li> </ul>
Labeling not uniform; lacking full warnings and precautions	Labeling uniform; carries extensive warnings and precautions

# European Experience

## European Medicines Agency (EMA)

- No current restriction of propoxyphene
- January 2008: EMA started a referral procedure regarding fixed combination of dextropropoxyphene and paracetamol
  - Initiated by the European Commission (EC) due to safety concerns related to overdose
  - EMA is to provide a scientific opinion:
    - Conducted a European-wide risk assessment
  - EC has 52 days to issue a final decision after EMA opinion provided
  - No decision has been adopted by the EC, according to EMA

# French Experience

- France has highest use rate of dextropropoxyphene and tramadol (a synthetic opioid used for moderate to severe pain)
- French National Commission for Pharmacovigilance investigated safety profile of medicinal products dextropropoxyphene and paracetamol combinations
  - Discussed results in 2007
  - A Scottish study showed a high rate of dextropropoxyphene suicide, but this rate not observed in France, which French Commission attributed to:
    - Cultural differences
    - Limited quantity of dextropropoxyphene in available products
  - Commission concluded there were no significant safety differences between propoxyphene products and codeine or tramadol
- France decided not to ban or further regulate dextropropoxyphene

# Abuse Liability & Addictiveness

- Proper management involves scheduling, not product removal
  - Many drugs with addictive properties can be safely and effectively used
  - Over 200 such drugs are scheduled as controlled substances
  - Drug Enforcement Administration (DEA), in 1977, made propoxyphene products Schedule IV, based on:
    - Low potential for abuse relative to Schedule III substances
    - Accepted medical use in treatment
  - DEA has not expressed any need for further restrictions

# Recommendations Against Use in Elderly Not Scientifically Supported

- Beers et al. “put propoxyphene among the drugs that are inappropriate for use in the elderly due to its lack of significant efficacy and high incidence of adverse effects”
- Methodological flaws of publication include:
  - Survey of 13 “experts” (credentials not given) hand-picked by the author, not the relevant scientific community
  - Petitioner Dr. Sidney Wolfe of Public Citizen was one of the experts
  - Only 2 analgesics were included, although many others of varying efficacy and safety could have been included
  - Questions worded with bias against propoxyphene

# Arizona Center for Education and Research on Therapeutics (CERT)

- Mission: To improve therapeutic outcomes and reduce adverse events caused by drug interactions and drugs that prolong the QT interval
  - Categorizes drugs to QT Drug Lists in consultation with QT Drugs Advisory Board; listed drugs reviewed on on-going basis
- Propoxyphene is not included among lists as definite association, possible association, conditional association, or as a concern to special population

Arizona CERT. *QT Drug Lists by Risk Groups*. Available at: <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm> (last accessed January 26, 2008).

# DAWN Death Data

- Petitioner presents Drug Abuse Warning Network (DAWN) data as it relates to causation and trends over time
- Causation: DAWN data do not provide a valid measure of deaths caused by a drug<sup>1</sup>
  - DAWN shows only that a drug is reported or “mentioned” by medical examiner in drug abuse death report
  - DAWN does not give drug quantities, only presence

1. See, e.g., Dept. of Health and Human Services, Substance Abuse and Mental Services Admin., Office of Applied Sciences, *Drug Abuse Warning Network Annual Medical Examiner Data 1999* (Dec. 2000).

# DAWN Death Data: Propoxyphene Mentions

- In 11,651 total drug abuse deaths in 1999, “propoxyphene” was mentioned 466 times (< 4%)
- Of the 466 propoxyphene mentions:
  - 5 reported propoxyphene alone
  - 325 reported multiple drugs
  - 34 reported drug and physiological condition
  - 58 reported drug and external physical event
  - 18 reported drug and medical disorder
  - 26 were unknown

Source: Dept. of Health and Human Services, Substance Abuse and Mental Services Admin., Office of Applied Sciences, Drug Abuse Warning Network Annual Medical Examiner Data 1999 (Dec. 2000).

# DAWN ED Data: Trending

- 2003 DAWN Report on Narcotic Analgesics showed the Emergency Department trend for 1994-2001
  - Propoxyphene mentions steadily decreased from 6,731 in 1994 to 5,361 in 2001
  - Narcotic analgesic mentions for every other drug in the class increased over this period
- Additional Emergency Department trends from DAWN
  - Propoxyphene mentions decreased to 4,676 in 2002
  - Mentions of propoxyphene alone decreased 53.9% from 1995 to 2002
  - Narcotic analgesic mentions continued to increase

Source(s): Dept. of Health and Human Services, Substance Abuse and Mental Services Admin., Office of Applied Sciences, *Drug Abuse Warning Network Annual Medical Examiner Data 1999* (Dec. 2000); Dept. of Health and Human Services, Substance Abuse and Mental Services Admin., Office of Applied Sciences, Drug Abuse Warning Network Database on *Emergency Department Trends from DAWN, Table 8.2.0* (2002).

# Summary

# Summary

- Propoxyphene products have a long history in the US of safe and effective use as labeled
- Propoxyphene products have been used continuously for a half century in multiple strengths, dosage forms, and combinations
- Propoxyphene products have well-characterized risks, of which practitioners are aware

# Safety of Propoxyphene Containing Products as Reported to the National Poison Data System (NPDS)

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# Options for Pain Management - Propoxyphene: Clinicians' Perspective

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# Options for Pain Management - Propoxyphene: Clinicians' Perspective

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Closing

# Closing

- Petitioner presents no credible scientific evidence that propoxyphene drugs present an imminent hazard to public health or that they are unsafe and ineffective when used according to approved labeling
- The safety and efficacy of propoxyphene have been reviewed and considered repeatedly by multiple US government agencies
  - HEW
  - FDA
  - VA

# Closing

- Petitioner raises no new safety or efficacy concerns that have not been previously considered and rejected by FDA
- Pain sufferers should not be deprived of the option of using propoxyphene products; these products should not be withdrawn as treatment options