History and Efficacy of Propoxyphene Products

Jin Chen, MD, PhD
Medical Officer
Division of Anesthesia, Analgesia & Rheumatology Products (DAARP)
CDER • FDA
Overview of Presentation

- Regulatory history of propoxyphene (PPX) products

- Efficacy of PPX products
  - Original NDA submissions in 1971
  - Literature reports
Regulatory History: 1957

The first propoxyphene products were approved based on safety only under the 1938 Food Drug & Cosmetic Act (FD&C Act)

- Darvon (propoxyphene HCl 32 mg and 65 mg)
- Darvon-Compound (aspirin, caffeine combination), discontinued in US
Regulatory History: 1962

Kefauver-Harris Drug Amendments to the 1938 FD&C Act required:

• Evidence of safety and efficacy to approve a new drug

• A retrospective efficacy assessment for drugs approved prior to 1962
  - FDA established the Drug Efficacy Study Implementation (DESI) program.
  - National Academy of Science-National Research Council (NAS-NRC) assessed the efficacy of all pre-1962 drugs

• Propoxyphene products underwent the DESI process in the 1960’s
Regulatory History: 1969

DESI notice published (amended in 1972) in Federal Register (FR): Darvon and its aspirin combination products were “effective for mild to moderate pain”

- The conclusion was primarily based on the recommendations of the NAS efficacy report.
- The NAS efficacy report relied upon two review articles published in the mid-1960s (Beaver 1966 and Lasagna 1964).

The FR publication (DESI conclusion), the NAS Efficacy Report and the published review articles are in Attachment-1 of Backgrounder-4.
Regulatory History: 1971

- Propoxyphene napsylate 100 mg was approved, trade-named “Darvon-N”
- Is molar equivalent to propoxyphene HCl 65 mg
- Was bioequivalent to propoxyphene HCl 65 mg (Darvon)
Regulatory History: 1972

- Propoxyphene/acetaminophen (PPX/APAP) combinations were approved
  - Darvocet: Propoxyphene HCl and acetaminophen
  - Darvocet-N: Propoxyphene napsylate and acetaminophen combination

- Efficacy trials and bioequivalence studies

- 90% Rxs of propoxyphene are the APAP combination products in current US market
Efficacy Data in 1971: NDAs of Darvocet and Darvocet-N

Seven single-dose efficacy trials were submitted to the Darvocet and Darvocet-N NDAs (Applicant: Eli Lilly & Company):

- Had identical study design
- Conducted by 3 external investigators
  - Lash for Studies 1, 2a & 2b
  - Bauer for Studies 3a & 3b
  - Johnson for Studies 4a & 4b
Study Design of the 7 Trials

- Randomized, double-blind, placebo-controlled, full factorial design

- Patients with mild to severe postpartum pain (normal delivery), n=30-48 each of 4 arms, received a single oral dose of:
  - Propoxyphene/acetaminophen (65/650 mg)
  - Propoxyphene (65 mg)
  - Acetaminophen (650 mg)
  - Placebo

- Efficacy was assessed hourly for 6 hours:
  - Time-course of analgesic effects (PID, PR) over 6 hr
  - $\text{SPID}_6$ (summed pain intensity difference over 6 hrs)
  - $\text{TOTPAR}_6$ (total pain relief score over 6 hrs)
Data Presentation of the 7 Trials

• Standard deviations for the efficacy data were not provided in the original study reports.

• Detailed statistical analyses for major analgesic outcomes (SPID$_6$ or TOTPAR$_6$) were not available in the report, there were only statement by the sponsor of statistical significance.

• The only statistical details shown in the original submission are limited to the first 2-hour post dose.

• The efficacy results differed across 7 trials
Time-course of PID: Study 3a (by Bauer) (Fig 4 in Appendix-2 of Backgrounder-4)

From original NDA submission of 1971
SPID$_6$ and TOTPAR$_6$ of Study 3a (by Bauer)

- PPX, APAP and the combination were statistically superior to placebo.

- PPX alone was comparable to APAP alone.

- The combination appears superior to PPX and APAP alone, but the statistical significance is unknown.
Time-course of PID: Study 3b (by Bauer)
(Fig 5 in Appendix-2 of Backgrounder-4)

From original NDA submission of 1971
SPID$_6$ and TOTPAR$_6$ of Study 3b (by Bauer)

- The combination and APAP alone, but not PPX alone, were statistically superior to placebo.
- The combination was numerically superior to APAP and PPX alone.
- APAP was numerically superior to PPX.
SPID$_6$ and TOTPAP$_6$

of Studies 1, 2a, 2b, 4a and 4b

The remaining 5 trials (conducted by different investigators) had similar results:

- PPX alone did not differ from placebo.
- The combination and APAP alone was statistically superior to placebo.
- The combination was comparable to APAP.
Time-course of PID: Study 1 (by Lash)
(Figs 1-3 & 6-7 in Appendix-2 of Backgrounder-4)

From original NDA submission of 1971
Summary of Efficacy Trials of 1971’s NDAs

- All 7 trials had the identical, single-dose, full-factorial design and were conducted using the same patient selection criteria.

- 5 of the trials showed that PPX alone had no statistically significant difference from placebo.

- APAP alone was statistically superior to placebo in all 7 trials.

- The combination was comparable to APAP alone and was statistically superior to placebo in 6 of 7 trials.
Efficacy Data in the Literature

- Literature search: PubMed and EMBASE databases (up to Dec 2008) and citations of relevant articles
- Identified the most relevant publications (drugs studied, adequacy of study design and data process/report)
  - 27 Randomized controlled trials (RCTs)
    - 17 acute pain trials
    - 10 chronic pain trials
  - 10 Systematic reviews (including meta-analyses)

These publications are summarized in Tables 1-3 in Appendix-1 of Backgrounder-4
Published RCTs

• Published between 1960s and 1970s

• The majority of the trials tested a single-dose of propoxyphene single-ingredient product in acute pain patients.

• There are limited literature reports of factorial design trials with the propoxyphene/APAP combination
  – One full factorial design trial
  – A few partial factorial design trials (PPX/APAP vs. APAP alone and/or placebo)
Published Reviews

• The reviews, including meta-analyses, all used similar published RCTs of propoxyphene products.

• The authors made similar conclusions:
  – Propoxyphene, as a single-ingredient product, was a weak analgesic.
  – Propoxyphene has no or little contribution to efficacy of the APAP combination for acute pain.
  – Limited information is available to assess analgesic effects on chronic pain.

• The conclusions were consistent with what we found from reviewing the individual trials in the literature.
Meta-Analysis (Moore et al, 2008)

(Cochrane Database Syst Rev: CD001440 (3), 2008)

• **Data source:**
  – 10 published RCTs
  – 1 previous meta-analysis (8 RCTs)

• **Adult patients with post-surgical moderate-to-severe pain received a single oral dose:**
  – Propoxyphene/APAP (65/650 mg)
  – Propoxyphene (65 mg)
  – Placebo

• **Standardized PI or PR to 50% of maximum SPID or TOTPAR across trials**

• **Outcome variables:**
  – RB: Relative benefit (vs. placebo)
  – NNTB: number-needed-to-benefit
  – Re-medication within 4-8 hours
## Meta-Analysis (Moore et al, 2008)  
*(Cochrane Database Syst Rev: CD001440 (3), 2008)*

**Propoxyphene vs. placebo**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative Benefit</th>
<th>Weight (%)</th>
<th>Relative Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berry 1975</td>
<td>26/73</td>
<td>18/76</td>
<td></td>
<td>30.0</td>
<td>1.50 [ 0.90, 2.50 ]</td>
</tr>
<tr>
<td>Bloomfield 1980</td>
<td>21/25</td>
<td>19/25</td>
<td></td>
<td>32.3</td>
<td>1.11 [ 0.84, 1.46 ]</td>
</tr>
<tr>
<td>Cooper 1986</td>
<td>16/50</td>
<td>10/56</td>
<td></td>
<td>16.1</td>
<td>1.79 [ 0.90, 3.58 ]</td>
</tr>
<tr>
<td>Coutinho 1976</td>
<td>8/15</td>
<td>6/15</td>
<td></td>
<td>10.2</td>
<td>1.33 [ 0.61, 2.91 ]</td>
</tr>
<tr>
<td>Trop 1979</td>
<td>9/25</td>
<td>1/25</td>
<td></td>
<td>1.7</td>
<td>9.00 [ 1.23, 65.85 ]</td>
</tr>
<tr>
<td>Van Staden 1971</td>
<td>5/26</td>
<td>6/29</td>
<td></td>
<td>9.7</td>
<td>0.93 [ 0.32, 2.69 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>214</strong></td>
<td><strong>226</strong></td>
<td></td>
<td>100.0</td>
<td><strong>1.48 [ 1.15, 1.90 ]</strong></td>
</tr>
</tbody>
</table>

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

Test for heterogeneity chi-square=8.40 df=5 p=0.14 I² = 40.5%

Test for overall effect z=3.01  p=0.003
**Meta-Analysis (Moore et al 2008)**

*(Cochrane Database Syst Rev: CD001440 (3), 2008)*

**PPX/APAP combination vs. placebo**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Relative Benefit</th>
<th>Weight (%)</th>
<th>Relative Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Cooper 1980</td>
<td>14/40</td>
<td>11/48</td>
<td></td>
<td>13.7</td>
<td>1.53 [0.78, 2.98]</td>
</tr>
<tr>
<td>Cooper 1981</td>
<td>24/42</td>
<td>6/37</td>
<td></td>
<td>8.7</td>
<td>3.52 [1.62, 7.67]</td>
</tr>
<tr>
<td>Evans 1982</td>
<td>15/30</td>
<td>8/30</td>
<td></td>
<td>10.9</td>
<td>1.88 [0.94, 3.75]</td>
</tr>
<tr>
<td>Honig 1981</td>
<td>17/50</td>
<td>9/48</td>
<td></td>
<td>12.5</td>
<td>1.81 [0.90, 3.67]</td>
</tr>
<tr>
<td>Moore 1997*</td>
<td>114/316</td>
<td>40/322</td>
<td></td>
<td>54.1</td>
<td>2.90 [2.10, 4.02]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>478</strong></td>
<td><strong>485</strong></td>
<td></td>
<td><strong>100.0</strong></td>
<td><strong>2.52 [1.99, 3.20]</strong></td>
</tr>
</tbody>
</table>

Total events: 184 (Treatment), 74 (Placebo)
Test for heterogeneity chi-square=5.14 df=1 p=0.27 P =22.1%
Test for overall effect z=7.59 p<0.00001

Meta-Analysis
(Po & Zhang: BMJ 1997)

• **Data source:**
  – 26 published RCTs

• **Adult patients with postsurgical pains received a single oral dose:**
  – PPX/APAP combination (65/650mg)
  – APAP (650 or 1000 mg)
  – Placebo

• **Outcome variables**
  – Standardized SPID
  – Response Rate Ratio (treatment vs. control)

• **Compare between the combination and APAP:**
  – Direct: head-to-head for factorial studies
  – Indirect: placebo-referenced cross studies
Meta-Analysis: Standardized SPID
(Po & Zhang: BMJ 1997)

- Difference in pooled SPID between the combination and APAP was not statistically significant.

- The combination and APAP were statistically superior to placebo in pooled SPID but with overlapping 95% CI, suggesting APAP was a primary contributor to the combination.
**Overall Summary**

Based on the evidence from DESI process, original NDA submissions and our literature review, we found that:

- Propoxyphene shows weak analgesic effects in some acute pain trials.

- The contribution of propoxyphene to the analgesic effects of the combination is variable across acute pain trials.

- With regard to chronic pain, the NDAs contain no data and there are insufficient data in the literature to assess the analgesic effects of propoxyphene products.