Pain, Obesity, and Alzheimer’s Disease: Public Citizen’s Efforts to Have FDA Ban Three Drugs

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Michael Carome, M.D.
Deputy Director
Public Citizen Health Research Group

Overview

• Introduction to Public Citizen and the Health Research Group (HRG)
• Pain: petition to ban the analgesic drug propoxyphene (Darvon, Darvocet)
• Obesity: petition to ban the weight loss drug sibutramine (Meridia)
• Dementia: petition to ban the Alzheimer’s disease drug donepezil, 23 mg dose (Aricept-23)

Introduction to Public Citizen and the Health Research Group

Overview of Public Citizen

• Serves as the people’s voice in the nation’s capital. Our overarching goal is to ensure that all citizens are represented in the halls of power
• Champion citizen interests before Congress, the executive branch agencies, and the courts
• Nonprofit organization that does not participate in partisan political activities or endorse any candidates for elected office; we accept no government or corporate money

Public Citizen – Five Policy Groups

• Congress Watch division
• Energy Program
• Global Trade Watch
• Health Research Group
• Litigation Group
Introduction to Health Research Group

- Founded by Ralph Nader and Sidney Wolfe in 1971
- Research-based, health advocacy group
- Petition the FDA to have unsafe or ineffective drugs and medical devices banned or re-labeled
- Petition OSHA to reduce worker exposures to hazardous chemicals and work conditions
- Educate the public about dangerous drugs and drug interactions through our newsletters and WorstPills.org
- Push state medical boards to do a better job disciplining doctors.
- Ardent champion of a single-payer, Medicare-for-all system.

http://www.worstpills.org/

Pain – Petition to Ban the Analgesic Drug Propoxyphene (Darvon, Darvocet)
Background - Propoxyphene (DPX)

- Centrally acting opiate analgesic
- First approved by the FDA in August 1957
- Developed by Eli Lilly and marketed under the brand names Darvon and Darvocet; later sold to Xanodyne Pharmaceuticals
- Metabolized in the liver to norpropoxyphene, which is more potent than propoxyphene
- With prolonged use, tolerance and physical dependence develop

First Petition to Ban Propoxyphene – 11/21/78

- Submitted to Joseph Califano, Secretary of HEW
- Requested either:
  - Ban immediately as an “imminent hazard” under the Food, Drug and Cosmetic Act; or
  - Reschedule as a Schedule II narcotic which would impose production quotas and prohibit refills
- DEA records: propoxyphene leads all other prescription drugs in the U.S. in drug-related deaths: 1974-1977: 2,154 propoxyphene-related deaths reported to the DEA

First Petition to Ban Propoxyphene – 11/21/78

- Eli Lilly misled physicians: introduced as a “non-narcotic,” “equal to codeine” in its pain-killing properties; has “fewer side effects than codeine”
- Properly controlled studies showed propoxyphene no more effective than aspirin and many show it to be less effective than aspirin, or in some cases, no more effective than placebo. Clearly less effective than codeine.
- The Medical Letter (1970): “many physicians are not sufficiently aware that coma, circulatory and respiratory depression, convulsions and death can result from overdose of propoxyphene, that the clinical picture is similar to that seen with narcotic drugs…”

Outcome: HEW denied the petition

Second Petition to Ban Propoxyphene – 2/28/06

- Submitted to the FDA Commissioner
- Propoxyphene has a cardiotoxic metabolite
- Toxicity develops at doses only slightly above the recommended daily dose, especially when combined with alcohol and other CNS depressants
- Associated with 7109 deaths, including 2110 accidental deaths, from 1981 through 1999
- Weak pain killer: propoxyphene plus acetaminophen not better than acetaminophen alone
- The United Kingdom announced a phased withdrawal of the drug in 2005
- 12th highest-selling generic drug in 2004 (23 million prescriptions)


- Propoxyphene-Related Death, 1981 - 2002
- Cumulative Deaths
- Deaths Per Year
Proportion of Deaths Involving Propoxyphene Classified by DAWN as Accidental, Suicide, or Unknown, 1981 to 1999

Second Petition to Ban Propoxyphene – 2/28/06
- Extremely low margin for safety
- Majority of propoxyphene dose is converted to norpropoxyphene (NPX)
- NPX is 2.5 X more potent than parent drug
- NPX has a half-life of 35 hours, 3 X longer than parent drug.
- Adverse cardiac effects of NPX: prolonged QRS complex (predisposing to ventricular arrhythmias), bradycardia (slow heart rate), asystole (no heart rhythm), decreased contractility (leading to heart failure), and hypotension.
- These adverse cardiac effects are not reversed by opiate antagonists such as naloxone

HRG Testimony at FDA Advisory Committee Meeting on Propoxyphene – 1/30/09

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- Evidence of cardiac toxicity in 222 Consecutive patients admitted to one Danish ICU with propoxyphene intoxication:
  - 107 (48%) heart failure
  - 12 (15%) asystole
  - 21 (9%) bradycardia
  - 91 (41%) abnormal ECG
  - 43(19%) QRS>120ms
  - 19 (8%) ventricular arrhythmia


HRG Testimony at FDA Advisory Committee Meeting on Propoxyphene – 1/30/09

- FDA conclusions concerning propoxyphene efficacy:
  - “…propoxyphene possesses weak analgesic effects in patients with acute pain compared to placebo…”
  - “…most of the studies show that in combination with acetaminophen, the propoxyphene component appears to contribute little or no additional analgesic effect beyond the efficacy of the acetaminophen when studied in patients with acute pain…”
Outcome of FDA Advisory Committee Meeting on Propoxyphene – 1/30/09

Based on the data presented, does the balance of risk and benefit support continued marketing of propoxyphene-containing products for the management of mild to moderate pain? (vote)

Yes: 12
No: 14

FDA Denies Second Petition to Ban Propoxyphene – 7/9/09

• In its denial of the petition, FDA stated it is “requiring... a clinical trial to assess the risk of cardiovascular events, including life threatening arrhythmias, that may occur in association with use of propoxyphene.
• On 8/6/09, HRG asked FDA Commissioner Margaret Hamburg to reconsider its 2006 petition, asserting FDA failure to consider all available scientific evidence and omitting or misrepresenting key information. Joined by former FDA Commissioner Donald Kennedy.

Propoxyphene – Final Belated FDA Action

• 11/19/10 FDA announcement:
  “Xanodyne conducted a study in healthy volunteers... Data from that study demonstrated that even when propoxyphene was taken at recommended doses, there were significant changes to the electrical activity of the heart including prolonged PR interval, widened QRS complex and prolonged QT interval.
  “In light of these new scientific findings, FDA determined the ...the overall balance of risk and benefit can no longer be considered favorable. The agency is recommending that propoxyphene products be removed from the US market.”

Propoxyphene – Final Belated FDA Action

• 11/19/10 FDA letter to Public Citizen’s HRG:
  “Although the agency is taking the action that you requested in your petition, it is doing so on the basis of data and studies that were not part of your original Citizen Petition. Thus, your [8/6/09] Petition for Reconsideration is hereby denied.”

Obesity – Petition to Ban the Weight Loss Drug Sibutramine (Meridia)

• Marketed by Knoll Pharmaceuticals/Abbott
• Approved November 1997 for the management of obesity, including weight loss and maintenance of weight loss, in conjunction with a reduced calorie diet
• Produces its therapeutic effects by blocking norepinephrine, serotonin and dopamine reuptake
First Petition to Ban Sibutramine – 3/19/02

- Pre-approval clinical trial data in study BPI 852 (1047 subjects): evidence of cardiovascular risk

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Sibutramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid heart rate</td>
<td>2.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>3.1%</td>
<td>1.2%</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>2.1%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

- Limited benefit: in obese subjects, average weight loss in comparison to placebo was 6.5 pounds in subjects taking 10 mg dose for one year

First Petition to Ban Sibutramine – 3/19/02

- FDA advisory committee (1996) voted 5 to 4 that the benefits of sibutramine did not outweigh the risks and also voted 8 to 0 that the pressor (high blood pressure-raising) effect of sibutramine was “clinically important.” [emphasis added]
- The FDA medical officer who reviewed the drug in 1996 wrote that “sibutramine has an unsatisfactory risk-benefit ratio and therefore this reviewer recommends non-approval of the original submission.” [emphasis added]

First Petition to Ban Sibutramine – 3/19/02

- Reports of serious adverse event submitted to the FDA Adverse Event Reactions (AERS) database following approval: 29 patient deaths, 19 with cardiovascular causes such as heart attacks.
- Included in the 19 cardiac deaths were 10 people who were 50 or younger, including three women under the age of 30.
- There were also 143 patients in whom an arrhythmia was reported.

Supplement to First Petition to Ban Sibutramine – 9/3/03

- Since petition filed, FDA AERS database has received reports of 30 additional cardiovascular deaths in patients taking sibutramine, bringing the total to 49. Twenty-seven of the 49 deaths (68%) were in people less than 50 years old.
- FDA Medical Officer (1996 review): “The extended use of sibutramine as currently proposed by the Sponsor, I feel, may likely subject a significant proportion of relatively healthy, overweight individuals to substantial risk of cardiovascular events.”

FDA Denies First Petition to Ban Sibutramine – 8/9/05

- Basis for denial: “An unbiased, objective assessment of sibutramine’s cardiovascular safety profile, particularly when used in obese patients with known or occult cardiovascular disease, can best be made through analyses of data from a large, randomized, controlled trial. The Sibutramine Cardiovascular Outcomes, or SCOUT study, is such a trial.” (SCOUT was ordered by the European Medicines Agency)
- FDA: SCOUT study was designed to show that weight loss with sibutramine and standard care was more effective than in reducing the # of cardiovascular events compared to weight loss from a placebo and standard of care.

Second Petition to Ban Sibutramine – 12/3/09

- SCOUT: randomized controlled trial involving 10,000 obese patients over age 55 with cardiovascular risks
- Early results of SCOUT reported by the FDA: increase in composite end point (MI, Stroke, resuscitated cardiac arrest or CV death) with sibutramine compared to placebo (statistically significant, p<.026, Fishers Exact test by HRG)
- By mid-2009, a total of 84 reports of deaths from cardiovascular causes in the FDA AERS database, including 30 in people 50 or younger. Of these 30 people, 11 were 30 or younger.
FDA’s Interim Response to Second Petition to Ban Sibutramine – 6/1/10

- “We are currently analyzing the SCOUT data submitted by Abbott.”
- “…before responding to your petition we intend to seek input from an advisory committee…in Fall 2010.”

HRG Testimony at FDA Advisory Committee Meeting on Sibutramine – 9/15/10

- Summarized data from prior petitions
- 1/21/10 European Medicines Agency decision to recommend ban of sibutramine: “…the benefits of sibutramine-containing medicines do not outweigh their risks…”
- Summary of SCOUT study results published in the New England Journal of Medicine on 9/2/10

HRG Testimony at FDA Advisory Committee Meeting on Sibutramine – 9/15/10

- Summary of key SCOUT study results

<table>
<thead>
<tr>
<th></th>
<th>Sibutramine (n=4906)</th>
<th>Placebo (n=4898)</th>
<th>Hazards Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome event*</td>
<td>11.4%</td>
<td>10.0%</td>
<td>1.16</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>4.1%</td>
<td>3.2%</td>
<td>1.28</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>2.6%</td>
<td>1.9%</td>
<td>1.36</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*composite of nonfatal MI, nonfatal stroke, resuscitation after cardiac arrest, and CV death

NEJM, 9/2/10

HRG Testimony at FDA Advisory Committee Meeting on Sibutramine – 9/15/10

- Lessons learned from the sibutramine fiasco:
  - The 1996 instincts/judgments of the FDA advisory committee and medical officer about increased cardiovascular risk of a drug that increases pulse, blood pressure and arrhythmias were correct.
  - The FDA’s zeal in 1997 to replace the recently-banned Redux (the fen of fen-phen) with another weight-reducing drug was dangerous.

- 8 of 16 committee members voted remove sibutramine from the market.

FDA Final Action on Sibutramine

- On October 7, 2010, the FDA requested that Abbott remove Meridia (sibutramine) from the U.S. market, and on October 8, 2010, Abbott agreed to voluntarily withdraw Meridia…from the U.S. market.
- January 5, 2011 letter to Public Citizen’s HRG: “…your petition requesting that FDA remove the weight loss drug Meridia (sibutramine) from the U.S. market is granted….after carefully evaluating the data from the SCOUT trial and other relevant data, we have determined that the risk-benefit profile of Meridia…is unfavorable.

Dementia – Petition to Ban the Alzheimer’s Disease Drug Donepezil, 23 mg Dose (Aricept-23)
**Background – Alzheimer’s Disease (AD)**

- Neurodegenerative disorder of uncertain cause
- Most common cause of dementia
- Estimated prevalence: 5.4 million patients in the U.S.
- A disease of older age; rarely occurs before age 60
- Memory deficits develop insidiously and progress slowly over time
- There is no cure; treatments are aimed at slowing progression, but current treatments offer minimal benefit
- Progresses inexorably; mean survival after diagnosis of AD ranges from 3 to 8 years

**Background – Donepezil**

- Inhibits acetylcholinesterase, an enzyme that breaks down the neurotransmitter, acetylcholine
- Marketed by Eisai Co Ltd. and Pfizer Inc.
- Approved November 1996 for mild to moderate AD at dose of 5 or 10 mg once daily
- Approved October 2006 for severe AD at a dose of 10 mg once daily
- Approved July 2010 for moderate to severe AD at a dose of 23 mg once daily (approval sought just as patent for the 5 and 10 mg doses was about to expire)

**Petition to Ban Aricept-23 – 5/18/11**

- In March 2007, FDA agreed to accept Eisai’s request for a single phase 3 study for the 23 mg dose of Aricept, under the following conditions: The current regulatory standard requires that the effectiveness of a treatment for [AD] be demonstrated on both a cognitive and a global (or functional) primary efficacy measure...Thus, [Study 326] can be considered to provide substantial evidence of effectiveness for the 23 mg/day dose...formulation of Aricept only if that dose is demonstrated to have a statistically significant superiority over the 10 mg/day dose of the immediate-release formulation on both primary efficacy measures, the [Severe Impairment Battery (SIB)] and the [Clinician’s Interview-Based Impression of Change-Plus (CIBC)]. [emphasis added]

**Petition to Ban Aricept-23 – 5/18/11**

- Study 326 – Primary efficacy endpoint results: change from baseline at 24 weeks

<table>
<thead>
<tr>
<th>Test</th>
<th>10 mg dose</th>
<th>23 mg dose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIB</td>
<td>0.4</td>
<td>2.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>CIBIC-Plus</td>
<td>4.3</td>
<td>4.2</td>
<td>0.18</td>
</tr>
</tbody>
</table>

- Secondary endpoints – No statistically significant differences between groups:
- AD Cooperative Study-Activities of Daily Living
- Mini-Mental Status Exam

**Petition to Ban Aricept-23 – 5/18/11**

- FDA medical reviewer conclusion regarding efficacy results from study 326:
  - “The results of study 326 did not satisfy the pre-specified criteria for demonstrating the efficacy of the higher dose of donepezil (23 mg QD).”

- FDA statistical reviewers cast doubt on strength of even the SIB efficacy data:
  - “There were more missing week 24 SIB data in the 23 mg...group than in the 10 mg...group (24% vs. 13%) and the 23 mg dropouts tended to dropout earlier than the 10 mg group.”
Petition to Ban Aricept - 5/18/11

• Study 326 – Safety results: Discontinuations for AEs

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>10 mg dose</th>
<th>23 mg dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Bradycardia</td>
<td>0.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>QT elongation</td>
<td>0.0%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Nervous System Dizziness</td>
<td>0.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Psychiatric Agitation</td>
<td>0.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Confusion</td>
<td>0.0%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

• Study 326 – Safety results: Most common AEs for all subjects (not just dropouts)

<table>
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<tr>
<th>Adverse Event</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3.4%</td>
<td>12%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.5%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.3%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.7%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Confusion</td>
<td>2.5%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

• FDA reviewer recommendations:

- Medical reviewer: “The results of Study 326 did not satisfy the pre-specified criteria for demonstrating the efficacy of the [23 mg] dose of donepezil…I recommend that this application…not be approved.” [emphasis added]
- Statistical reviewers: “…the data from [study 326] does not seem to provide enough support for the efficacy of the 23 mg [dose].”

• Medical literature review of acetylcholinesterase inhibitors reveals following problems:

- Neuropsychiatric: agitation, aggression, nightmares, Pisa syndrome
- Cardiovascular: bradycardia, heart block, syncope
- Urologic problems: urinary incontinence

• Dr. Russell Katz, Director of the Division of Neurology Products, wrote the FDA summary review:

- “…no statistical significance between the treatments on the primary measure of overall functioning, [and] a clear lack of significance on another accepted measure, the ADCS-ADL [a secondary endpoint],”
- “There is a clear increase in the incidence of adverse events on the 23 mg dose compared to the 10 mg dose.”
- “These [AEs] are not trivial events in these patients; these could lead to significant morbidities and even increased mortality…[these events] are of particular concern, given that these patients had all been receiving treatment with 10 mg once a day for at least three months.”
Petition to Ban Aricept-23 – 5/18/11

- Nevertheless, Dr. Katz approved Aricept-23 over the objections of the medical and statistical reviewers.
  - Dr. Katz posed the question: “Does the absence of a demonstration of any superiority of the 23 mg dose to the 10 mg dose on measures of overall functioning, coupled with the increased incidence of potentially significant adverse events, argue against the approval of this product?” His answer was “The 23 mg dose is clearly superior to the 10 mg dose on the cognitive measure [SIB]. In my view, this strongly argues for a conclusion that the 23 mg dose is very likely to also have an effect on overall functioning [CIBIC-Plus], despite this not having been demonstrated directly in this study.”

Take Home Messages

- Persistence in health advocacy eventually can pay off.
- FDA too often approves drugs despite evidence of limited benefits and serious safety signals.
- FDA is too slow to act to remove dangerous products from the market, frequently acting years after their regulatory counterparts in other countries (e.g., UK and Europe) act.
- Thousands of preventable deaths in the U.S. have resulted from FDA’s delays in removing dangerous and minimally effective drugs from the market.
- Senior FDA officials sometimes overrule the recommendations of the expert FDA reviewers who spent the most time analyzing the data.

Contact Information

Telephone: 202-588-7781
Email: mcarome@citizen.org
Websites: www.citizen.org
          www.citizen.org/hrg
          www.citizen.org/hrgpublications
Address: Health Research Group
         Public Citizen
         1600 20th Street, N.W.
         Washington, D.C. 20009