Regulatory Issues for Approval of New Weight Loss Drugs

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Conflicts

CPC Clinical Research (University-based Academic Research Center) has received grant support from numerous industry sponsors, but none relevant to this presentation

William Hiatt has no other conflicts on this topic and does not receive funds personally from any industry sponsor
Obesity Epidemic

NHANES 2012 obesity data
Men BMI = 28.7, obesity prevalence = 35.5%
Women BMI = 28.7, obesity prevalence = 35.8%
Children prevalence of obesity = 16.9%

JAMA 2012;307(5):491-7
JAMA 2012;307:483-90

What are the Goals for Obesity?

Patients often want cosmetic benefit defined as weight loss per se, look better, feel better

Providers want clinical benefit defined as:
• Reduce mortality
• Prevent and treat diabetes
• Prevent and treat cardiovascular disease
  • Associated blood pressure and lipids
• Treat sleep apnea and lower blood pressure
• Treat degenerative arthritis
What Works?
(what has proven clinical benefit)

• Lifestyle (diet and exercise)
• Bariatric surgery
• Drugs?

My bias is to challenge the role of pharmacotherapy

The current perspective was derived from 2010-2012 FDA meetings on new weight loss drugs and summarized in several publications

Circulation 2012;125:1171-7
JAMA 2012;308:1099-1100

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Look AHEAD

ILS=Intensive Lifestyle Intervention
DSE=diabetes support and education
Arch Intern Med 2010;170:1566-75
Look Ahead Outcomes

Trial completes 2014 but after 1 year:

- 8.7 Kg reduction in weight
- 21% improvement in fitness
- 3 mg/dl increase HDL cholesterol
- 5 mg/dl reduction in LDL cholesterol
- 7 mmHg reduction SBP
- 0.6 reduction hbA1c

Diabetes Care 2011;34:2152-57

Diabetes Prevention Program

Diabetes Prevention Program

NEJM 2002;346:393-403
Diet Composition does not matter

Lifestyle Interventions

Look Ahead and DPP
- Very high compliance
- Sustained weight loss over 4 years
- Cardiovascular benefits pending
Bariatric Surgery and Mortality

Bariatric surgery and Diabetes

JAMA 2012;307:56-65

NEJM 2012;366:1567-76
Role for Weight Loss Drugs?

Lifestyle (diet and exercise) effective but not efficacious
Bariatric surgery works for extreme obesity
Obesity epidemic continues and patients want options
FDA has determined that 5% net weight loss by lifestyle is clinically meaningful but at what cost?

FDA Criteria for Weight Loss Drug Approval?

Weight loss of 5% (mean or categorical)
And…FDA obesity drug guidance 2007 links a reduction in fat mass to clinical benefit:
- Reduced morbidity and mortality
- “through quantifiable improvements in biomarkers, such as blood pressure, lipids and HbA1c”
- Therefore weight loss alone not sufficient

FDA Weight Management Guidance 2007
Current Weight Loss Drugs

Sibutramine (approved 1997) – sympathomimetic with effects on NE, serotonin and B3 receptors

Phentermine/Topiramate (Qnexa) - Phentermine is sympathomimetic to reduce food intake and increase thermogenesis. Topiramate treats seizures and migraines with unclear weight loss mechanism

Naltrexone/Bupropion (Contrave) – is an opioid receptor antagonist with a NE and dopamine receptor inhibitor

Lorcaserin (Lorcress) – activates 5-hydroxytryptamine 2c receptors

Drug Induced Weight Loss

Circulation 2012;125:1171-77
CV Risk of Weight Loss Drugs

Sympathomimetic drugs have a mechanism of CV risk
- Sibutramine
- Phentermine/topiramate
- Naltrexone SR/Bupropion SR

5-hydroxytryptamine drugs have valvulopathy and pulmonary hypertension risks
- Fenfluramine
- Lorcaserine

Cardiac risk events low frequency but devastating

How Does a Trial Evaluate Safety?

- Adverse and serious adverse event reporting (AE/SAE)
- Evaluated at each study visit by spontaneous patient reporting
- Medical dictionaries code AE/SAE’s to common terms that lack specificity
  - Cardiac ischemic events reported as “angina”, “acute coronary syndrome”, “heart attack”, “myocardial infarction”, “chest pain”
  - Most common events may be non-informative “headache”, “fatigue” and mask less common but more critical safety signals
Targeted Safety Evaluation

- If drug mechanism has specific, targeted risk then trial will employ specific AE/SAE adjudication
- Independent, blinded Clinical Events Committee (CEC)
- CEC reports adjudicated events to independent and often unblinded Data Safety Monitoring Board (DSMB)
- DSMB reports to independent Steering Committee regarding trial conduct
- Examples, major and minor bleeding with new antithrombotic drugs (clopidogrel, prasugrel, dabigatran)

FDA Guidance Evaluating CV Risk
Diabetes Drugs

- Establish independent CV endpoints committee
- Adjudicate all CV events from all phase 2 and 3 trials
- Meta-analysis and prospective analysis plan
- Upper boundary of 2-sided 95% CI of risk < 1.8
- Risk ratio < 1.3. If 1.3-1.8 then additional safety study (phase 4) required
- New development programs may be subject to greater scrutiny

CDER Guidance Dec 2008
Exclusion of Risk Approach
Cilostazol as a Symptomatic Rx for PAD

Brass and Hiatt, Clin Pharmacol Ther 2006;79:165-72

Event Table to Exclude Risk

<table>
<thead>
<tr>
<th>Relative risk to be excluded (% increase)</th>
<th>1.10 (10%)</th>
<th>1.25 (25%)</th>
<th>1.50 (50%)</th>
<th>1.75 (75%)</th>
<th>2.00 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of events required in both groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80% Power</td>
<td>2722</td>
<td>497</td>
<td>150</td>
<td>79</td>
<td>51</td>
</tr>
<tr>
<td>90% Power</td>
<td>3771</td>
<td>688</td>
<td>208</td>
<td>109</td>
<td>71</td>
</tr>
<tr>
<td>95% Power</td>
<td>4765</td>
<td>869</td>
<td>263</td>
<td>138</td>
<td>90</td>
</tr>
</tbody>
</table>

Operating assumption that sponsors can combine all phase 2 and phase 3 trials based on prospective design considerations (especially populations) and proportional hazards assumptions
Sibutramine
FDA Approval 1997

Efficacy included 26 studies < 24 weeks, 20 long-term, patients low risk for CV events
Efficacy = 4% mean placebo-adjusted weight loss

<table>
<thead>
<tr>
<th></th>
<th>Sibutramine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV events</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Therefore no hint of safety concern and FDA agreed
Post approval excess CV events reported in Europe
European regulators mandated phase IV safety study

SCOUT
Sibutramine Cardiovascular Outcomes Trial

Enrolled patients at increased CV risk
- Diabetes with additional CV risk factor (n=2385)
- H/O cardiovascular disease (n=1552)
- Diabetes + CV disease (n=5807)
- Duration 3.4 years, but only 58% completed on Rx
- Primary endpoint = MI, CVA, vascular death, resuscitated cardiac arrest

Sibutramine Weight Loss

- Mean Body Weight (kg)
  - Placebo
  - Sibutramine

Study Visit

Sibutramine Hemodynamics
Pulse

- Mean Pulse Rate (bpm)
  - Sibutramine
  - Placebo

Study Visit
Sibutramine CV Risk

Cardiovascular Risk by Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.16</td>
<td>1.03-1.31</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.01</td>
<td>0.74-1.38</td>
</tr>
<tr>
<td>CV disease</td>
<td>1.28</td>
<td>0.92-1.78</td>
</tr>
<tr>
<td>DM &amp; CV disease</td>
<td>1.18</td>
<td>1.02-1.37</td>
</tr>
</tbody>
</table>

P for interaction 0.56
Sponsor argued to change product label to exclude CV disease
But risk generalizable to entire study population
No other subgroups or strategy identified to mitigate risk
Sibutramine Outcome

FDA voting question: minor label change, major label change (limited use, black box) or remove from market

16 voting members, 8 to remove, 8 to retain on market (2 with minor label change!!)

One month later FDA reports sponsor ‘voluntarily’ agreed to withdraw drug from market (could there have been any other outcome?)

Drug Cardiac Risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Weight Loss From Baseline, %</th>
<th>MACEs, No. (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug</td>
<td>Placebo</td>
<td>Mean Difference, %</td>
</tr>
<tr>
<td>Epitramine/phenetermine&lt;sup&gt;a&lt;/sup&gt; 10% Diabetes</td>
<td>-10.9</td>
<td>-1.6</td>
<td>-9.4</td>
</tr>
<tr>
<td>No diabetes</td>
<td>-9.8</td>
<td>-1.2</td>
<td>-8.6</td>
</tr>
<tr>
<td>Nalhexone/propazine&lt;sup&gt;b&lt;/sup&gt; No diabetes, study No. 1</td>
<td>-6.1</td>
<td>-4.9</td>
<td>-4.8</td>
</tr>
<tr>
<td>No diabetes, study No. 2</td>
<td>-6.3</td>
<td>-5.1</td>
<td>-4.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-6.0</td>
<td>-1.8</td>
<td>-4.2</td>
</tr>
<tr>
<td>Lorazepam&lt;sup&gt;c&lt;/sup&gt; Study No. 1, no diabetes, BLOOM</td>
<td>-5.8</td>
<td>-2.2</td>
<td>-3.7</td>
</tr>
<tr>
<td>Study No. 2, no diabetes, BLOOM</td>
<td>-5.8</td>
<td>-2.8</td>
<td>-3.0</td>
</tr>
<tr>
<td>Diabetes, BLOOM/DM</td>
<td>-4.5</td>
<td>-1.5</td>
<td>-3.1</td>
</tr>
<tr>
<td>Sibutramine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-6.4 kg</td>
<td>-1.6 kg</td>
<td>-4.8 kg</td>
</tr>
</tbody>
</table>

JAMA 2012;308:1099-1100
Obesity Drug Outcomes

Sibutramine - withdrawn

Phentermine/Topramate (Qnexa) – Approved with post approval commitment for large CV outcomes trial

Naltrexone/Bupropion (Contrave) – Denied with pre-approval CV outcomes trial requirement

Lorcaserin (Lorcess) – Approved with post approval CV outcomes trial commitment