Cardiovascular Safety Assessments: An FDA Perspective

Patrick Archdeacon, MD
Senior Clinical Adviser
Office of Medical Policy, CDER/FDA
February 19, 2014
Disclaimer

The opinions and conclusions expressed in this presentation are those of the presenter and should not be interpreted as those of the FDA.
OMP Interests

- Understand the appropriate criteria for determining when a CVSOT may be required for a specific product or class of products (e.g., those with a shared mechanism of action)
- Understand the appropriate criteria for determining when CVSOT may be required for all products developed for an indication/therapeutic area
- Allowing for appropriate consideration of differences in benefit-risk ratios and patient preferences across the spectrum of clinical contexts, understand whether those criteria are applied consistently across the Center
The Role for CVsOTs

- Pivotal Phase 3 trials powered to evaluate efficacy; often incapable of determining whether true differences exist in safety profiles across study arms
- Safety data not only often lack statistical power, but are also often imperfectly collected
- In many (most?) therapeutic areas, efficacy endpoints alone have a limited capacity to definitively inform a benefit-risk assessment
- Non clinical and clinical studies as well as mechanism of action and drug class may suggest the possibility of a safety signal that cannot be fully evaluated in the context of a pivotal phase 3 efficacy trial
However, CVSOTs also have limited ability to fully inform B:R analyses

- MACE events are not the only set of clinically important SAEs imperfectly captured during Phase 2 and Phase 3 trials – outcomes like cancers, hepatic injury, congenital defects, non-MACE cardiovascular SAEs, etc are typically imperfectly described by data from pivotal trials
- While well-designed CVSOTs will provide best answer to a narrowly defined question, it is likely that residual safety questions may remain (e.g., related to population, indication, and/or dose effects)
Examples of CVSOTs that have factored into FDA considerations

• PRECISION
  – Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen

• RECORD
  – Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycemia in Diabetes

• SCOUT
  – Sibutramine Cardiovascular OUTcomes
PRECISION

- Naproxen vs ibuprofen vs celecoxib in patients at risk of AMI (initiated in 2005 at FDA request)
- About 27,000 patients enrolled as of 12/2013
- Estimated completion date: ~mid-2016
- Discussed at CRAC meeting on 2/10-11/2014. Per Pink Sheet report, Committee members generally favored continuing study (no formal vote on this question).
- “I think the best chance to characterize the differential risk among non-steroidals is the PRECISION trial, for all its warts...” Dr Sanjay Kaul, CRAC member, cardiologist at UCLA (Pink Sheet Daily, Feb 11, 2014)
NSAID Safety Review: FDA Panel Seeks Continued PRECISION From Pfizer

By Sarah Karlin  /  Email the Author  /  View Full Issue
Word Count: 961  /  Article # 14140211006  /  Posted: February 11 2014 11:45 PM

Executive Summary

Pfizer’s long-term safety outcome study comparing Celebrex, ibuprofen and naproxen has its flaws, but FDA advisory committee says its data will be far superior to meta-analyses or observational studies.
RECORD

• RECORD trial started in 2001 to evaluate equipoise around differences CV risk factors and unclear clinical significance of predisposition to fluid retention with rosiglitazone

• Unplanned interim analysis of RECORD data in 2007 helped put additional context around other emerging rosiglitazone data and analyses

• 2008 FDA guidance on evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes and with recommendations of EMDAC, where no specific safety signal exists
3. It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk. (vote yes/no requested).

Yes: 14  No: 2  Abstain: 0
FDA Guidance December 2008

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes
FDA NEWS RELEASE

For Immediate Release: Nov. 25, 2013
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@hhs.fda.gov
Consumer Inquiries: 888-INFO-FDA, druginfo@fda.hhs.gov

FDA requires removal of certain restrictions on the diabetes drug Avandia

The U.S. Food and Drug Administration today announced it is requiring the removal of certain restrictions on prescribing and use of the diabetes drug Avandia (rosiglitazone) to reflect new information regarding the cardiovascular risk of the medicine. Today’s actions are consistent with the recommendations of expert advisory committees.

Results from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) clinical trial showed no elevated risk of heart attack or death in patients being treated with Avandia when compared to standard-of-care diabetes drugs. These data do not confirm the signal of increased risk of heart attacks that was found in a meta-analysis of clinical trials first reported in 2007.

“Our actions today reflect the most current scientific knowledge about the risks and benefits of this drug,” said Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation and Research. “Given these new results, our level of concern is considerably reduced; thus, we are requiring the removal of certain prescribing restrictions.”
SCOUT

- SCOUT trial started in 2003, completed in 2009
- 10,744 subjects (9,804 randomized after lead-in period)
- Sibutramine noted to increase blood pressure and pulse in some patients, leading to concern of possible cardiovascular risks
- FDA draft guidance for industry from 2007 ("Developing Products for Weight Management") recommends that "it may be appropriate for some weight-management products to have specialized safety assessments" but does not recommend CVSOTs for all products
- Abbott voluntarily stopped marketing sibutramine in US at request of FDA, based on FDA review of SCOUT data
FDA Drug Safety Communication: FDA Recommends Against the Continued Use of Meridia (sibutramine)

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary

Safety Announcement

[10-8-2010] The U.S. Food and Drug Administration (FDA) is recommending against continued prescribing and use of Meridia (sibutramine) because this drug may pose unnecessary cardiovascular risks to patients. FDA has requested that Abbott Laboratories—the manufacturer of Meridia—voluntarily withdraw this drug product from the United States market. Abbott has agreed to voluntarily stop marketing of Meridia in the United States.

Meridia was FDA-approved in November 1997 for weight loss and maintenance of weight loss in patients with a body mass index (BMI) greater than or equal to 30 (≥30) kg/m² or for patients with a BMI ≥27 kg/m² who have other cardiovascular risk factors. BMI is a measure of body fat in adults that is based on height and weight. Patients with a BMI ≥30 kg/m² are considered obese.

FDA’s recommendation is based on new data from the Sibutramine Cardiovascular Outcomes (SCOUT) trial, which demonstrated a 16% increase in risk of major adverse cardiovascular events (a composite of non-fatal heart attack, non-fatal stroke, resuscitation after cardiac arrest and cardiovascular death) in patients treated with Meridia compared to patients taking a placebo (see Data Summary below). At the end of the trial (60 months), patients in the Meridia group lost a small amount of body weight compared to patients in the placebo group.
3. (VOTE) Do you believe that obesity drugs **without** a theoretic risk or signal for CV harm should be required to rule out a certain degree of excess CV risk with a CVOT or an appropriately sized meta-analysis of phase 2 and 3 MACE data?

Vote: Yes: 17  No: 6
Observations regarding CVSOTs

• CVSOTs have demonstrated significant value for the evaluation of preliminary safety signals

• Routine use of CVSOTs in absence of defined safety signals has been endorsed for some therapeutic areas, but not others
  – FDA acknowledges and even embraces some variation in approaches to its reviews
  – Differences may reflect clinical contexts (e.g., differences in feasibility, differences in unmet medical needs, differences in underlying biology supporting general concern, etc), HOWEVER...
  – Consequences to differing standards: in practice, therapeutic areas are in competition with one another for research resources

• While context may vary across TAs, principles and criteria for requiring a CVSOT should be the same.