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Quick Pulse

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New Study Finds Significant Heart Attack Risk with Diabetes Drug

A Vioxx-Type Controversy with GlaxoSmithKline's Avandia?

GlaxoSmithKline's diabetes drug, Avandia (rosiglitazone), has all the elements of a bad novel: A drug used by millions of people worldwide, data that the drug is dangerous, the company defending it amid suggestions of a cover-up, an uncertain FDA, and a congressional committee investigating. Among the questions being asked are:

- ***Does Avandia really increase the risk of heart attacks and death?*** A prominent cardiologist says it does, the company denies it, and the FDA is unsure.
- ***Has GSK been as forthcoming as it should have been?*** The company reportedly alerted the FDA as early as 2005 that there was a signal of a problem and gave the Agency a meta-analysis in 2006 which raised concerns, but GSK did not warn doctors or patients.
- ***Why has the FDA been so slow to interpret the data?*** The FDA has had the full GSK dataset since August 2006 and still hasn't completed its analysis nor made any conclusions. It hopes to finalize its study soon and hold a public hearing within a couple of months. But it wasn't the FDA that made this problem public. And how long would it have taken for the FDA to act if an independent meta-analysis hadn't been published?
- ***How will patients and doctors react?*** **Will patients switch to insulin or to newer drugs, such as Merck's Januvia (sitagliptin) and Novartis's Galvus (vildagliptin)?** Patients already are calling their doctors, but even the professional societies don't have much useful advice yet except to "discuss it with your doctor."
- ***What will the FDA ultimately decide to do?*** Stay tuned. You may know in a few months.

GSK claims Avandia has a 37% share of the oral glycemic control market. By one estimate, 11 million prescriptions were filled for Avandia in the U.S. in 2006 alone – and the drug has been on the market for 8 years.

Data Suggest Avandia is Dangerous

Dr. Steven Nissen (past president of the American College of Cardiology) and Kathy Wolski MPH, both of the Cleveland Clinic, performed a meta-analysis of 42 clinical trials of Avandia that were more than 24 weeks in duration. The study was published in the ***New England Journal of Medicine*** on Monday, May 21, 2007. In the meta-analysis Avandia, a thiazolidinedione (TZD) approved by the FDA in 1999 for the treatment of hyperglycemia in Type 2 diabetes, increases the risk of myocardial infarction (MI) and perhaps cardiovascular (CV) death.

Dr. Nissen and Ms. Wolski did not call for the immediate removal of Avandia from the market, but they did say there is an "urgent need" for comprehensive evaluations to clarify the CV risks of Avandia, including a review of all of GSK's source data by an external academic coordinating center and a review by the FDA of all data.

The known side effects of Avandia – and the other drug in this class of PPAR-γ agonists, Takeda's Actos (pioglitazone) – are weight gain, edema, anemia, and liver toxicity. Rosiglitazone is also sold in two combination products: GlaxoSmithKline's Avandamet (with metformin) and Avandryl (with glimepride). CV outcomes are particularly important for drugs taken for diabetes because >65% of diabetics die from CV causes. An FDA official said the safety concerns with Avandia also apply to Avandamet and Avandryl.

The meta-analysis (which included the DREAM and ADOPT trials) looked at 14,560 patients on Avandia and 12,283 on comparators. Among the findings:

- Avandia "may be capable of provoking MI or death from CV causes after relatively short-term exposure."
- The mechanism for the increased CV risk remains uncertain, though it could be related to these known factors:
  - Adverse effect on serum lipids. The label says the mean LDL increase is 18.6% at 8 mg for 26 weeks vs. placebo.
  - Congestive heart failure precipitation (and volume overload).
  - Modest reduction in hemoglobin.
- The findings may not be a class effect, since the large, prospective PROactive trial found Actos was significantly better than placebo (p=0.027) on the ***secondary*** endpoint of combined MI, stroke, and death, though it only trended better (p=0.095) on the primary endpoint of combined coronary and peripheral vascular events. Actos also has "more favorable effects on lipids, particularly triglycerides" than Avandia.

Cleveland Clinic Meta-Analysis of Avandia

Measurement	Odds ratio (number of events)		p-value
	Avandia	Control	
Primary endpoint #1: MI	1.43 (86 events)	(72 events)	0.03
MI vs. placebo	1.80	---	0.07
Primary endpoint #2: CV death	1.64 (39 deaths)	(22 deaths)	0.06 *
CV death vs. placebo	1.22	---	0.55
MI in all small trials	1.45	---	0.15
MI in DREAM trial	1.65	---	0.22
MI in ADOPT trial	1.33	---	0.20
CV death in small trials	2.40	---	0.02
CV death in DREAM trial	1.20	---	0.67
CV death in ADOPT trial	0.80	---	0.67

*** Described as "borderline significant."**

- The FDA should reconsider the use of blood glucose measurements as surrogate endpoints for approval of new diabetes drugs.

In an accompanying editorial, Dr. Bruce Psaty of the University of Washington and Dr. Curt Furberg of Wake Forest University compared Avandia to Merck's Vioxx (rofecoxib) – which was withdrawn from the U.S. market in 2004 due to CV risks – saying Vioxx "represented a similar regulatory failure to insist on large trials of public health importance in a timely fashion." Remember: Dr. Nissen warned about the dangers of Vioxx three years before it was taken off the market.

Dr. Psaty and Furberg called for "regulatory action" by the FDA, concluding:

- "On the basis of this meta-analysis…the possibility of CV benefit associated with the use of rosiglitazone seems remote."
- "In view of the potential CV risks and in the absence of evidence of other health advantages…**the rationale for prescribing rosiglitazone at this time is unclear**."
- "Rosiglitazone represents a major failure of the drug-use and drug-approval process in the U.S."
- Avandia was approved on the basis of short-term studies, using a surrogate marker (glycemic control), and the FDA should have demanded large, long-term, randomized Phase IV (post-marketing) clinical trials.
- The FDA's approach to Phase IV studies has been "desultory."
- Patients should discuss their concerns with their doctor, not stop taking Avandia unilaterally.

There are both strengths and weaknesses to the meta-analysis:

- **Strengths**
  1. Effort to include unpublished studies.
  2. Use of major CV events and the primary endpoint.
  3. Analysis comparing Avandia to placebo (as well as to other diabetes medications).

- **Weaknesses** (which were described as "substantial")
  1. The trials included were not originally intended to look at CV outcomes, and CV outcomes generally were not centrally adjudicated.
  2. The definitions of MI in the trials were not available.
  3. Patient-level data were not used.
  4. No dose-response analysis was possible.
  5. The trials included both placebo and active-treatment comparators.
  6. There was no standard method of identifying or validating outcomes, so events or ineligible trial may have been missed or misclassified.
  7. The total number of events was relatively small.

In an interview, Dr. Psaty said that the data were the weakness in Dr. Nissen's study. The ideal study, he said, "should come from a large, well-designed, long-term study of rosiglitazone after approval. The company didn't do that. The FDA didn't ask for that. This is why, eight years into this drug on the market, we are now identifying a cardiovascular risk." Dr. Psaty was very critical of the FDA, "My concern is that the FDA isn't currently protecting the health of the public with its approval process…I absolutely agree that the threshold for approval should not be just a biomarker (serum glucose) but should be real clinical benefit. In this case (Avandia) you not only didn't get real benefit, you got real risk."

GlaxoSmithKline Defends Avandia

GlaxoSmithKline issued a response, defending the safety and efficacy of Avandia and saying it "strongly disagrees" with the meta-analysis conclusions: "The totality of the data show that Avandia has a comparable cardiovascular profile to other oral anti-diabetic medicines. GSK stands firmly behind the safety of Avandia when used appropriately, and we believe its significant benefits continue to outweigh any treatment risks."

GSK criticized meta-analyses in general as "not the most rigorous way" to reach definitive conclusions about adverse events. The company also charged that Dr. Nissen's analysis was "based on incomplete evidence" and a methodology with "significant limitations."

A better way to look at safety, GSK claimed, is through the long-term clinical trials of Avandia that are ongoing, including RECORD – which the data safety monitoring boards are allowing to continue, indicating they have not seen a significant negative side effect. RECORD is a large, long-term, prospective clinical trial in diabetics which was initiated in 2000.

Perhaps a little surprisingly, GSK cited the ADOPT and DREAM trials in support of Avandia. GSK said those trials found the overall risk of serious cardiovascular events (CV death, MI, and stroke) with Avandia was comparable to metformin and sulfonylurea (glyburide), though there was a numerically higher rate of MI with Avandia. However, it was the MI rate in the DREAM trial that made Dr. Nissen start to worry about Avandia.

ADOPT Results

Measurement	Avandia	Metformin	Glyburide
MI	1.65%	1.38%	0.97%
CV death	0.34%	0.28%	0.56%

GSK provided the FDA with both its own 42-trial meta-analysis (some of these trials, but not necessarily all, were the same as those used by Dr. Nissen) and an observational analysis from a managed care database of >33,000 diabetics. GSK did not release the findings of its meta-analysis, but it said the observational database found no difference in ischemic cardiovascular events (including MI) with Avandia compared to other oral anti-diabetic medicines.

The FDA Still Studying its Response

Dr. Robert Meyer, director of the FDA's Office of Drug Evaluation II in the Center for Drug Evaluation and Research (CDER), said the FDA is "aware of a potential safety issue related to Avandia (rosiglitazone)," but the FDA has not yet decided whether the risk is significant or what to do about it. Dr. Meyer said, "There is a ***potentially*** significant increase in the risk of heart attack and heart-related deaths in patients taking Avandia. However, other published and unpublished data...provide contradictory evidence about the risks…I think we don't have a clear regulatory or even clinical advice message today, given the data available to us." He said that the FDA is not asking GSK to take any specific actions at this time, and patients with underlying heart disease or who are at high risk of heart attack should talk to their doctor about the new information.

The FDA reportedly first got preliminary data from GSK's meta-analysis in September 2005 but waited until it got GSK's completed meta-analysis in August 2006 before beginning its own patient-level review of the data. GSK offered the meta-analysis; it hadn't been requested by the FDA. After taking a quick look at the GSK data in 2006, Dr. Meyer said the FDA decided the "robustness was not sufficient for regulatory decision, and we needed to re-analyze the complex dataset ourselves to make a better informed decision…We had some issues with the way it had been done by GSK, and we wanted to do a more robust analysis."

Has the FDA acted as quickly as it could or should have done? Dr. Meyer said, "I believe we have...There is a risk in short-term uncontrolled diabetes, and we've tried to weigh the risks of going forward with an uncertain message and the possibility of hundreds of thousands of patients may be having to switch therapy."

The FDA review is "in the later stages" but not yet complete. Dr. Meyer declined to characterize the Agency's preliminary findings except to say, "The FDA has not confirmed the clinical significance of the reported increased risk in the context of other studies…We felt the current data…would stand until we got a better handle on all the data to make a more informed decision…We wanted to wait for a better analysis…to make a more informed discussion. In the meantime, we got other, contradictory data…We have not been in a position where we thought we could define or have a meaningful public discussion." Dr. Meyer indicated the FDA analysis should be completed in the very near term," and there will be an Advisory Committee meeting within "a couple of months."

Among the other points FDA officials made about Avandia were:

- **Competitors.** The FDA doesn't know yet whether Takeda's Actos (pioglitazone) has a similar risk, and the FDA has asked Takeda to do a similar meta-analysis of the Actos trials. The Takeda- and Lilly-sponsored PROactive study, which was presented at the European Society of Diabetes (EASD) meeting in 2005, looked at the safety of high-dose (45 mg) Actos. The trial missed its primary endpoint, but Actos did show a 16% reduction in the secondary endpoint of a composite of death, stroke, and MI. However, Actos also was associated with a doubled risk of heart failure in that trial. FDA officials called this trial "neutral." Dr. Meyer said, "I'm not sure one can reach a conclusion that the safety of rosiglitazone is different from pioglitazone."
- **Labeling.** The potential risk of heart attacks and chest pain already was in the Avandia label before the FDA got the (completed) meta-analysis from GSK. Since Avandia was approved, the FDA has been monitoring several heart-related adverse events (e.g., fluid retention, edema, and congestive heart failure).
- **GSK meta-analysis.** The GSK meta-analysis given to the FDA showed a possible 30%-40% increased risk of CV adverse events. Dr. Meyer said, "These data, if confirmed, would be of significant concern since patients with diabetes are already at an increased risk of heart disease."
- **FDA analysis incomplete.** The FDA analysis of the GSK data does show "some increased risk." However, Dr. Meyer said other data "would lead to a quite different conclusion, so we don't feel there are consistent enough data to make a firm conclusion."
- **Deaths.** The FDA would not speculate on any deaths that may have resulted from Avandia. Dr. Meyer said, "At this point we don't feel that there is consistent enough data to make a firm conclusion from a regulatory standpoint, and I don't think there is enough data to make a...conclusion about the meaning or the risk that Dr. Nissen has provided. So without being able to reach a firm conclusion, I wouldn't speculate on excess deaths as they relate to risk, if in fact it does exist…We don't have a final estimate at this time."
- **FDA future action.** The FDA is not excluding any possible regulatory action at this point. Dr. Meyer added, "We are not excluding any potential regulatory pathways."
- **Contradictory data.** The observational database provided by GSK "did not show an increased risk" and interim analyses of the ongoing Avandia RECORD trial are "quite reassuring."
- **Biomarkers.** The FDA remains committed to the use of hemoglobin A_{1c} (HbA_{1c}) as a surrogate biomarker. Dr. Meyer said, "HbA_{1c} is one of the best developed surrogate markers we have because of the DCCT and the UKPDS trials (which) strongly support (the conclusion that) control of glycemia leads to improved outcomes. Most of those outcomes are in microvascular disease – retina, kidney, and nerves – but there are suggestions that long-term control of glycemia also improves CV outcomes…I don't think on the basis of what we have now that we would say HbA_{1c} is not a reasonable surrogate… HbA_{1c} remains a reasonable endpoint for assessing oral hyperglycemics."
- **Benefits of Avandia.** There are short-term benefits of glycemic control beside CV outcomes, including avoiding hyperosmolar coma or elevated infection rates.
- **Pathway for new drugs.** The FDA hasn't figured out the path forward for other companies or drugs in the diabetes space, but Dr. Meyer advised, "If one started planning a study today, the likelihood of meaningful results in the next 8-10 years is relatively low…So, a randomized clinical trial may not be the best way to proceed…One alternative is to use analytical techniques, observational studies."

The FDA's advice to patients and doctors was: "If they are taking Avandia and, particularly if they have underlying heart disease or are otherwise at risk (i.e., a pre-existing condition), they should talk to their doctor…the patients who may want to talk about their situation with their doctors are those who had a past MI or other heart disease or who are at particularly high risk otherwise."

The Patient Dilemma

American Diabetes Association (ADA) vice president for clinical affairs Sue Kirkman said that the ADA is receiving many calls from worried patients, "The ADA, ACC (American College of Cardiology, and the AHA (American Heart Association) will issue a joint press release. We are urging people to talk to their physicians about their own treatment for diabetes because this is obviously very early, and we're just finding out about it as well. It was kind of an after-the-fact analysis of studies that weren't really designed to look for cardiovascular outcomes. We feel it is concerning and needs further study by the FDA and others, but right now we're recommending that people stay calm, talk to their doctor, and figure out the best course for themselves."

Dr. Ira Goldfine, an endocrinologist at the University of California, San Francisco's Diabetes Center, said that he probably will not put new patients on Avandia but also will not take patients off it who are doing well on the drug, "Avandia is a very potent drug for diabetes…A lot of people are taking this drug, and we need to know if this is a class effect or not…Does Actos do the same thing?" Meanwhile, he is telling his patients, "Be patient…Hold still for a while until we get more information…We have to be alert and see what happens…I wouldn't panic at this point."

Dr. Goldfine pointed out that stopping Avandia abruptly might hurt a patient, and a week or two wouldn't make a big difference. He said he doesn't want to see Avandia taken off the market, but also doesn't want to see his patients at risk, "Most diabetic patients have a three-fold risk for having heart attacks – coronary artery disease – and roughly 67% die of it, so most patients are at risk."

Dr. Athena Philis-Tsimikas, executive director and chief medical officer of The Whittier Institute for Diabetes in La Jolla CA, said that she probably won't put new patients on Avandia until more is known, "We have to take it very seriously and demand an evaluation." As for the many patients she has on Avandia, Dr. Philis-Tsimikas said she will have to decide what to do on a case-by-case basis, "We have a huge number of people on Avandia – huge. Right now, we have to tell them that the FDA is evaluating this further. We can't tell people to come off or stay on at this point. We're waiting to see if someone can evaluate and then advise us on whether they should stay on. We have no other drug that acts like (Avandia) in its category of drugs…When I think about my patients, and that's my major concern, this is enough to take a closer look and evaluate it on a case-by-case basis with my patients. If I'm worried, I may take them off it."

Dr. Philis-Tsimikas said that there are alternatives for patients who want to stop taking Avandia, "The most important thing we have to do is make sure that their blood sugar stays under control." She said that the number one cause of death in Type 2 diabetics is heart disease, "I see it all the time, and I don't want it to happen more often than it would because I gave someone a drug that made it happen…(But) if you start pulling drugs and blood sugar goes up, that has consequences as well." The Whittier Institute for Diabetes website tells patients to stay on Avandia for now, but if they have further questions to talk to their doctor.

Dr. Sidney Wolfe, Director of Health Research Group at Public Citizen, said, "We strongly urge patients – as we have for almost 2.5 years – not to use this drug." He said the meta-analysis shouldn't have come as a surprise, "In animal studies done prior to its approval, one of the most constant findings was damage to the heart, and within the first six years of approval, there were 689 cases of heart failure reported to the FDA in patients using the drug. In addition, there have been reports of anemia which, along with heart failure, which increases the risk for a heart attack...We have warned readers on **WorstPills.org** since the end of 2004 that they should not use this drug. More recently, there have been numerous reports of visual abnormalities in the form of macular edema and increases in several kinds of fractures in women." At best, he said, Avandia should be "a last-choice treatment for Type 2 diabetes. In addition to the accumulating evidence of its risks, it is not even as effective as other diabetes drugs in lowering blood sugar or HbA_{1c}."

Dr. Wolfe also claimed the FDA knew five years ago about the dangers associated with Avandia. He said an internal FDA memo dated July 16, 2002, shows that FDA scientists recommended that the label for both Avandia and Actos should include reports of heart failure in patients taking those drugs. The memo reportedly cites 47 adverse reaction reports – 25 with Avandia and 22 with Actos – that resulted in hospitalization for heart failure. Dr. Wolfe said the number of heart failure hospitalizations increased to 803 as of fall 2006 (415 for Avandia and 388 for Actos).

Dr. Wolfe urged the FDA either to put a black-box-warning on the drugs or to ban them altogether. He said, "The failure of the FDA to act on the recommendations made almost five years ago by its Division of Drug Risk Evaluation is yet another case in which the conclusions of scientists who are engaged in post-market drug safety review are not taken seriously enough or addressed soon enough."

CONGRESS IS NOT HAPPY

Both the House and Senate are considering bills with measures that would reform the FDA at least somewhat, and action is expected before September 2007. The Avandia drama may impact how this legislation gets finalized.

House hearing

In a directly related move, Cong. Henry Waxman (D-CA), chairman of the House Oversight and Government Reform Committee, said that he plans to hold a hearing on June 6, 2007, on the FDA's role in evaluating Avandia's safety. Invited witnesses include Dr. Steven Nissen, FDA Commissioner Dr. Andrew von Eschenbach, and GSK CEO Dr. Jean-Pierre Garnier. An FDA official declined to say whether Dr. von Eschenbach or any other FDA official would testify.

Rep. John Dingell (D-MI), chairman of the House Committee on Energy and Commerce, and Rep. Bart Stupak (D-MI), chairman of the Energy and Commerce subcommittee on Oversight and Investigations, also are investigating GSK's and the FDA's handling of Avandia. In a statement, Rep. Dingell said, "We learned from an FDA briefing that the Agency has known about this problem for at least eight months and perhaps even longer. What we don't know is why diabetics and their doctors haven't been notified of the substantial risk to the heart from a drug prescribed to protect the cardiovascular system…It is incredible that the Agency charged with protecting the public health has such a poor record when it comes to post market drug safety…Regrettably, it is incidents like this that demand legislative changes in the way FDA deals with drug safety. The Committee will address these dangerous shortcomings while writing legislation to reauthorize PDUFA."

Rep. Stupak added "FDA's apparently callous disregard for the safety of diabetics taking Avandia is very reminiscent of the Agency's failure to move on Vioxx when substantial safety signals first became known. Like Vioxx, Avandia may

have unnecessarily risked the lives of tens of thousands of Americans." He noted that the FDA has been "less than cooperative with the Oversight efforts on drug and food safety issues," adding, "The FDA is on notice that we have reached the end of our rope on their stonewalling of investigations into their failures to keep Americans safe from dangerous drugs and poisonous foods. We are going to find out who in the FDA knew about the dangers of Avandia, what they knew, and when they knew it. If the Commissioner's Office and the Center for Drugs think that we will tolerate delays and misinformation regarding Avandia like they have attempted in the Ketek matter and other Committee inquires, they are sorely mistaken."

Rep. Dingell and Rep. Stupak, along with Rep. Waxman, Rep. Joe Barton (R-TX), Rep. Ed Whitfield (R-KY), and Rep. Tom Davis (R-VA) wrote to FDA Administrator von Eschenbach about Avandia more than two weeks ago. Those letters are available at:
http://energycommerce.house.gov/Press_110/110-ltr.050407.FDA.vonEschenbach.Avandia.pdf

http://energycommerce.house.gov/Press_110/110-ltr.043007.FDA.von%20Eschenbach%20.Avandia.pdf

Senate investigation

Sen. Max Baucus, chairman of the Senate Finance Committee, and Sen. Chuck Grassley, the ranking member of that committee, sent a joint letter to the FDA asking what it knew about Avandia and when the Agency learned about it. They also sent a joint letter to the president of U.S. pharmaceuticals for GSK, Christopher Viehbacher, asking the company to respond to allegations that company executives sought to silence an independent scientist(s) about the risks of Avandia. The senators want FDA and GSK officials to come before their committee and answer questions.

- Sen. Baucus said, "What we are learning about the handling of Avandia by both GlaxoSmithKline and the FDA is appalling and unacceptable. Both the drug company and the FDA have some major explaining to do about what they knew about Avandia, when they knew it, and why they didn't take immediate action to protect patients. The No. 1 priority for drug manufacturers and the FDA must be patient safety. Medicare and Medicaid patients – and all Americans – must never be put at risk like this again."
- Sen. Grassley said, "We need to know if this is another Vioxx, where the FDA sat on its hands and endangered lives. The FDA has talked a good game about how it's beefed up post-market surveillance over the last two years, but a case like this undermines that claim. It'll take more than administrative reforms to fix the system within the FDA. Congress ought to take advantage of the opportunity that we have right now with the FDA funding bill to make a real difference for public safety. Study after respected study has said that the FDA office responsible for post-market review of drug safety ought to have equal footing with the FDA's drug approval office. It's hard to understand how there's any resistance to this kind of reform if you care about public safety and public access to the never ending flow of new information about pharmaceuticals. I won't stop making the case for giving the post-market review office real clout."

Excerpts from the senators' letter to FDA Commissioner von Eschenbach:

- "Since the Food and Drug Administration (FDA/Agency) approved Avandia in 1999, physicians have written tens of millions of prescriptions for the drug. This could mean tens of thousands of cardiovascular adverse events attributable to this drug."
- "It is troubling, to say the least, that by taking Avandia, diabetics may be increasing their risk of the very adverse event that they hope to prevent by controlling their blood sugar. To make matters worse, American taxpayers have spent hundreds of millions of dollars on this drug through the Medicare and Medicaid programs."
- "The committee has received reports that executives with GSK met with FDA officials in October 2005 and later in August 2006 after further exploring these cardiovascular problems. We understand that during the same time period, other concerns were raised by FDA employees."
- "On May 9, 2007, Dr. Steven Galson, director of the Center for Drug Evaluation and Research, testified before Congress that FDA guidance approved in March should protect the public against problems with pharmaceuticals such as what we are now seeing with Avandia…Dr. Galson's testimony flies in the face of FDA's leisurely reaction to GSK's briefing over a year ago on cardiovascular problems attributed to Avandia."
- "It appears that the new guidance on communicating drug safety information has not improved the FDA's ability to protect the American people in a timely manner."

The senators sent the FDA a list of eight questions and set a deadline of June 4 for the Agency to answer:

1. When did you first become aware that Avandia may cause a higher incidence of myocardial infarctions, cardio-vascular disease, and/or cardiovascular death?
2. Given the effects of Avandia on blood glucose levels and other cardiovascular risk factors like cholesterol levels and body weight, did the FDA consider requiring GSK to conduct a long-term randomized trial to demonstrate risks and/or benefits such as how Avandia affects heart attack risk? What were the discussions, if any, around this issue at the FDA? Did the FDA make the suggestion to GSK? If so, what was GSK's response? Please provide a complete account of the evolution of these discussions, including related communications, documents, and records.

3. How did the FDA first become aware of this problem? Describe in detail FDA's actions to address this problem.

4. Please provide a formal, detailed timeline of your agency's actions regarding Avandia beginning with the date on which FDA staff first became aware of this higher incidence of cardiovascular problems related to Avandia and/or were notified by GSK of these problems. This timeline should identify, among other things, any internal or external communications and/or meetings, including meetings with GSK. Please provide relevant documents and/or records.

5. Describe in detail actions that the FDA has taken to investigate the potential for Avandia to cause cardiovascular problems since FDA was first advised or became aware of such risks.

6. Please provide all documents and/or records regarding Avandia since your agency first began examining whether patients taking the drug might be at a higher risk for myocardial infarctions, cardiovascular disease, or cardiovascular death.

7. Please identify all agency personnel (including full name, title, and contact information) who have examined the issue of Avandia and myocardial infarctions, cardiovascular disease, and/or cardiovascular death. Also, explain what role they played in investigating and/or communicating that Avandia may cause these adverse reactions. In responding to this question, please include internal and external communications.

8. When did the FDA first learn of the study and/or work of Dr. Steven Nissen, one of the authors of the ***New England Journal of Medicine*** article, regarding Avandia and myocardial infarctions? Please provide all communications, documents and records, both internal and external, regarding Dr. Nissen's study and/or work on Avandia.

In their letter to GSK, the senators made many of the same comments as they did to the FDA, but they added some other concerns, including:

- "One of the most immediate concerns to us are reports that GSK employees silenced one or more medical professionals who attempted to speak out about the potential for cardiovascular problems with Avandia. This allegation is very serious and warrants further investigation."
- "We request a briefing for our committee staff, focusing in particular on: (1) allegations that GSK executives sought to silence medical professional(s) regarding possible serious adverse events related to Avandia, and (2) the reports and any other information that GSK provided to the FDA regarding adverse events related to Avandia."

The senators' questions to GSK were similar, though slightly different, to those posed to the FDA. GSK was given an extra week to respond, with a deadline of June 11th.

1. When did GSK first become aware that Avandia may cause a higher incidence of myocardial infarctions, cardiovascular disease, and/or cardiovascular deaths? How did GSK first become aware of this problem?

2. Describe in detail what actions GSK took to address this problem. Please include copies of all responsive documents. In responding to this inquiry, please be specific as to what raised GSK's suspicion that people taking Avandia might be at a higher risk for cardiovascular problems.

3. When it was approved, or soon after, there was evidence that Avandia improved the control of blood glucose but had adverse effects on other risk factors like weight and cholesterol. An important scientific question is whether Avandia thus reduces or increases the risk of heart attack in diabetics. Answering this question would require a large long-term randomized trial with heart attack as one potential outcome. Please provide all communications, documents, and records relevant to a discussion on conducting such a trial, from the time that the New Drug Application was first submitted to the FDA. Did GSK conduct such a trial? If not, why not? What were the arguments for and against conducting such a trial? What was the decision-making process regarding such a trial?

4. Please provide a detailed timeline of GSK's actions regarding Avandia beginning with the date on which your company first became aware of the potential for a higher incidence of cardiovascular problems related to the use of Avandia and the time GSK notified the FDA of such potential. This timeline should identify specifically, among other things, any internal or external communications and/or meetings, including meetings with the FDA. Please provide relevant documents and/or records.

5. Please identify all GSK personnel (including full name, title, and contact information) who have examined the issue of Avandia and myocardial infarctions, cardiovascular disease, and/or cardiovascular death. Also, explain what role they played in investigating and/or communicating that Avandia may increase the risk of these adverse reactions. In responding to this question, please include internal and external communications.

6. Please provide any and all contracts or similar instruments between GSK and any outside scientists/medical professionals regarding Avandia and efforts to either directly or indirectly limit that individual's ability to discuss adverse events related to Avandia. For each contract or similar instrument, please provide all related documents, records, and/or communications.

7. Please identify any and all third parties (e.g., corporations, individuals, universities, etc.) engaged by GSK to examine, review, evaluate or analyze Avandia and/or the effects of its use. Please be sure to include the nature of the work performed and provide a copy of any and all draft and final products provided to GSK.

8. When did your company first learn about the study and/or work of Dr. Steven Nissen on Avandia and cardiovascular problems? Please provide all communications, documents and records, both internal and external, regarding Dr. Nissen's study and/or work on Avandia, including any consultants who may have been hired to examine/discuss Dr. Nissen's work.

PUTTING THE AVANDIA DATA IN CONTEXT

To put the Avandia findings in some perspective, remember that Bristol-Myers Squibb's Pargluva (muraglitazar), a dual PPAR-γ/PPAR-α agonist, was rejected by the FDA because of an increase in CV events, including MI. Here are some data on two other drugs with late findings of CV risk: Vioxx and Wyeth's Prempro – a fixed-dose combination of Premarin (conjugated equine estrogen) and Cycrin (medroxyprogesterone acetate).

TAKEDA'S Actos. The PROactive trial of high dose (45 mg) Actos vs. placebo missed its primary endpoint. The trial was powered to show a 20% improvement in time from randomization to first occurrence of any cardiovascular event (defined as the composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, coronary revascularization, revascularization in the leg, or amputation above the ankle), but it showed only a 10% improvement (21.0% Actos vs. 23.5% placebo, p=.095).

Actos did show a 16% reduction in the major secondary endpoint – the composite of heart attacks, stroke, and premature death (12.3% Actos vs. 14.1% placebo, p=0.027) – but Actos also was associated with a ***doubled*** risk of heart failure. Each of the composites of the primary and secondary endpoints except one trended in favor of Actos, but did not meet statistical significance in any of these measurements considered alone, though an investigator said the trial was not powered to show a difference in the individual measurements. Leg bypass was the one exception; it was slightly worse with Actos.

The study chairman, Dr. John Dormandy, Professor of Vascular Science at St. Georges Hospital, University of London, U.K., estimated that adding Actos to other diabetic medications in 1,000 people would avoid 21 first MIs, strokes, or deaths. Looked at another way, 48 patients would need to be treated for three years to avoid one first major cardiovascular event.

A COMPARISON OF AVANDIA AND ACTOS

A Takeda-sponsored study also presented at EASD 2005 compared edema and weight gain with these two agents when given as monotherapy over 24 weeks, and the results were mixed.

PROactive Metabolic Results

Measurement	Actos	Placebo	p-value
Metabolic results			
HbA_{1c} change from baseline	-0.8%	-0.3%	<.001
TGL	-11.4%	+1.8%	<.001
HDL	+19.0%	+10.1%	<.001
LDL	+7.2%	+4.9%	.003
LDL/HDL ratio	-9.5%	-4.2%	<.001
SBP change from baseline	-3.0	0	0.033
Weight change	Up 3.6 kg	Down 0.4 kg	<.05

Results of the PROactive Trial

Measurement	Actos	Placebo
Discontinuations	427 patients	438 patients
Primary endpoint #1: All-cause mortality, non-fatal MI, stroke, acute coronary syndrome, coronary revascularization, revascularization in the leg, or amputation above the ankle	21.0% (p=.095)	23.5%
Principal secondary endpoint: All-cause mortality, non-fatal MI, or stroke	12.3% (p=.0273)	14.4%

Other PROactive Results

Measurement	Actos	Placebo
Heart failure leading to death	0.96%	0.84%
Symptoms of hypoglycemia	27.9%	20.1%
Symptoms of hypoglycemia requiring hospitalization	0.7%	0.4%
Edema in the absence of heart failure	21.6%	13.0%

Takeda-sponsored Study Comparing Actos and Avandia

Measurement	Actos n=369	Avandia n=366	p-value
Mean change in HbA_{1c}	~ Down 0.7	~ Down 0.6	.129
Mean change in triglycerides	~ Down 12%	~ Up 15%	<.001 favoring Actos
HDL	~ Up 15%	~ Up 8%	<.001 favoring Actos
LDL	~ up 15%	~ Up 23%	.002 favoring Avandia
Mean weight change over time	~ Up 4.4 pounds	~ Up 3.5 pounds	.164
Change in pedal edema from baseline to Week 24			
Worsening edema	13.4%	12.8%	Nss
Improving edema	5.8%	7%	Nss
No change	18.1%	15.1%	Nss
No edema	62.7%	65.1%	Nss

MERCK'S Vioxx, from the FDA's Cardio-Renal Advisory Committee in 2005:

Merck Presentation on GI and CV Risk of Vioxx

Measurement	Relative Risk	p-value
VIGOR Trial		
CV thrombotic events of Vioxx vs. naproxen	2.38	.002
Time to confirmed upper GI event	0.46	<.001

WYETH'S Prempro, from National Insitute of Health's 2002 Workshop on the Women's Health Initiative findings:

Relative Risk of Coronary Heart Disease (CHD)

Age	Prempro	Placebo
50-59	0.21%	0.13%
60-69	0.35%	0.28%
70-79	0.71%	0.60%

WHI Results as of April 30, 2002

Measurement	Prempro events per 10,000 patient-years	Placebo events per 10,000 patient-years	Prempro events vs. placebo	Relative risk of Prempro vs. placebo
Primary endpoint: Coronary heart disease: non-fatal MI and CHD death	37	30	7 more	29% increase
Stroke	29	21	8 more	41% increase
VTE	34	16	22 more	112% increase
Primary adverse endpoint: Breast cancer	38	30	8 more	26% increase
Colorectal cancer	10	16	6 fewer	37% reduction
Endometrial cancer	54	50	4 more	Nss
Hip fracture	10	15	5 fewer	33% reduction
Global Index (balance of risk:benefit)	170	151	19 more	12% increase
Total deaths	231	218	15 more	Nss

Source: Journal of the American Medical Association

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