Tegaserod: is there a class safety issue?

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Outline

• Current FDA B-R Assessment Framework
• Scope of Symptomatic GI Diseases
• Pre-specification/Quantification of CV Risk
  – Notes from the Nov 2011 GIDAC meeting
  – What are we asking for?
• Considerations
  – Platelet article
• Comments on Dr. Anderson’s conclusions
# FDA Risk Benefit Framework

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<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tr>
<td>Analysis of Condition</td>
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<td>Current Treatment Options</td>
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<td>Benefit</td>
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<td>Risk</td>
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<td>Risk Management</td>
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**Benefit-Risk Summary and Assessment**
# Scope of Symptomatic GI Diseases

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<tr>
<th>GERD</th>
<th>FUNCTIONAL DYSPEPSIA</th>
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<tr>
<td>• Est. 10% of population experiences symptoms daily</td>
<td>• Est. 35-44 M (US) with symptoms</td>
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<tr>
<td>• Est. 20-25% of patients (6-8 in US) do not obtain adequate relief</td>
<td>• Major subtype is postprandial distress syndrome (PDS) defined by</td>
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<td>from stomach acid-reducing treatments</td>
<td>– Postprandial fullness</td>
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<td>– Early satiety, or</td>
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<td>– Upper abdominal bloating</td>
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<tr>
<th>GASTROPARESIS</th>
<th>LOWER GI INDICATIONS</th>
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<tr>
<td>• Est. 5M people (US) with symptoms</td>
<td>• Est. 36 people (US) with chronic constipation</td>
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<td>• High prevalence in diabetic patients</td>
<td>• Est. 5.5 M adults (US) suffer from IBS with constipation</td>
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<td>• No existing therapies adequately meet this patient need</td>
<td>• Est. 28M adults (US) suffer form IBS with intermittent constipation</td>
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<td>• Opioid induced chronic constipation</td>
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Should B-R be Pre-Specified?

In general it is helpful to the review division to have an idea of the boundaries of acceptable BR considerations during product development and review

• **Efficacy:**
  – Quantitative outcomes are well defined and agreed upon for many products and specified in protocols.
  – Quantifying outcomes for some programs may be difficult:
    • When diseases lack validated outcome measures
    • When numbers of patients with disease are small
    • When there is a lack of natural history data

• **Safety:**
  – Quantitative pre-specification can be challenging
    • Level of evidence, sources, uncertainties
Risk Quantification/Pre-Specification Example: GIDAC Advisory Committee

Cardiovascular Safety and the Serotonin (5-hydroxytryptamine) Receptor 4 (5HT4) Agonists Class

November 2011 Meeting
GIDAC Advisory Committee Meeting
November 2011

**Issue:** past history regarding members of the class and cardiovascular safety

**Purpose:** the design and size of premarketing cardiovascular safety development programs necessary to support approval of products in the class of serotonin (5-hydroxytryptamine) receptor 4 (5HT4) agonists for the proposed indications of:

- chronic idiopathic (of unknown cause) constipation (CIC),
- constipation predominant irritable bowel syndrome (IBS-C),
- gastroparesis, and
- gastroesophageal reflux disease that does not respond to a proton pump inhibitor.
Considerations for Cardiovascular Safety Evaluations in non-Cardiac Drug Products

1. Cardiovascular safety in the drug class
2. Nonclinical and Phase 1&2 clinical evaluations
3. Unmet medical need
4. Population for which drug is being developed (context of use)
5. Assessment of efficacy and safety (Risk/Benefit Assessment)

(November 2011 FDA AC slide)
GI Experience with 5-HT4 Agonist Class

• Cisapride (Propulsid – 1993-2000)
  – Cardiac arrhythmias (QT prolongation) associated with Drug-Drug Interactions due to metabolic pathway (cytochrome P450)

• Tegaserod (Zelnorm - 2002-2007)
  – Excess ischemic cardiovascular events

Both Drugs are no longer on the market in the U.S.

(November 2011 FDA AC slide)
GI Experience with 5-HT4 Agonist Class

• Thorough QTc evaluation prior to approval works well in GI drug evaluation.

• For CV risk where drugs will be used chronically in symptomatic GI diseases:
  – Is there zero risk tolerance for CV events related to drugs that treat Symptomatic GI Diseases?
  – Is ICH recommendation for long-term safety assessment enough pre-approval? (100 patients exposed for a year)
  – Should a study be done to rule out increase risk of MACE?
    • What size should it be/ what RR should be R/O?
    • How long should the study be?
  – What type of REMS should we have for a CV safety issue? How can we mitigate the risks?
Statistical Considerations for Design of CV Safety Studies

Dedicated, randomized cardiovascular (CV) outcome trials

– Gold standard for determining the hazard ratio (HR)
– Comparison of an investigational treatment relative to a well understood control.
– Typically designed as event-driven trials to rule out an excess risk measured by an upper bound of a 95% confidence interval for the hazard ratio.

Non-enriched populations with a relatively low CV event rate require more patient years compared to enriched populations to be studied

– To observe the same number of CV events and
– To achieve the same statistical power for a pre-specified hazard ratio margin.

(November 2011 FDA AC slide)
Statistical Considerations for GI Drug Development

• The number of patients or patient years required to observe a defined number of events depends on the background risk.
  
  – **Non-enriched population**: observational study of Tegaserod (Zelnorm) suggests the rate of CV events (MI or stroke) is between 1 and 3 per 1000 patient years¹ in a population with 80% women and 75% under 55 years old.
  
  – **Enriched population**: population with CV risk factors and an estimated rate of CV events between 10 and 20 per 1000 patient years.

Sample Size Scenarios with 90% Power in an Enriched Population

(November 2011 FDA AC slide)
For new products in the class, can nonclinical, clinical pharmacology, and clinical data, such as those presented for the newer 5-HT4 agonists, dispel (i.e., alleviate the need for a “dedicated” safety study) the cardiovascular safety concerns (e.g., prolonged QT interval, ischemic events) raised by the clinical safety experience of the previously approved 5-HT4 agonists?

– If yes, specify on which data you are relying.
GIDAC Question 1 Answer

Votes: Yes: 14 No: 8 Abstain: 0

“Members who voted “Yes” felt the unmet need for medications in these patient populations and the lack of a strong signal for cardiovascular toxicity outweighed the potential risks. Members commented that assumptions for these new agents appeared to be made based on older agents in the class, but were not convinced that cardiovascular toxicity is a class effect. However, members expressed lingering concerns for the potential of drug-induced cardiovascular toxicity, but felt that those concerns could be addressed in studies to evaluate efficacy and a “dedicated” safety study was not necessary”.

“Members who voted “No” felt that the potential for cardiovascular toxicity was apparent and additional safety studies were necessary to dispel concerns.

In general, members agreed that high-risk for cardiovascular disease patient populations should be included in studies in order to obtain a true index of cardiovascular risk. In addition, it was noted that the heterogeneous nature of these patient populations warranted further review of the cardiovascular safety of these agents when used in with other medications”.


Among the uses for which 5-HT4 agonists are being developed, (chronic-idiopathic constipation, constipation predominant irritable bowel syndrome, gastroparesis, other functional motility disorders), is there an indication for which you would be unwilling to accept an increased cardiovascular risk?

a. If yes, specify on which data you are relying
b. For those that are willing to accept an increased risk, state the level of risk you would find unacceptable (e.g., Hazard Ratio).
GIDAC Question 2 Answer

Yes: 9 No: 11 Abstain: 2

“Members who voted “No” were inclined to accept an increased cardiovascular risk depending on the severity of the condition. Several members noted that the ultimate decision would have to be made by the patient”.

“Members who voted “Yes” felt that for chronic-idiopathic constipation and possibly other functional motility disorders, they would not be willing to accept an increased cardiovascular risk because of the availability of other treatment options. Members noted, however, that for gastroparesis and possibly constipation predominant irritable bowel syndrome, they would be more willing to accept an increased cardiovascular risk”.

Question 3 and Answer

Does the Committee recommend a “dedicated” cardiovascular safety trial (a trial in which the primary objective is to define cardiovascular risk) to demonstrate the safety of 5-HT4 agonists?

Yes: 4 No: 17 Abstain: 1

“Members who voted “Yes” felt that rising concerns of cardiovascular safety with other agents on the market justifies a “dedicated” safety trial in these new agents. Several members noted that such trials are feasible and further assessment of these agents in high risk populations is necessary”.

“Members who voted “No” voiced concerns about potential cardiovascular side effects, but still felt that a “dedicated” cardiovascular safety trial was not necessary. Several members mentioned that post-marketing observation was essential to catch any potential signals for cardiovascular toxicity. In addition, the feasibility of such trials was questioned and concerns about costs were raised. Members who voted “No” also recommended that the efficacy trials conducted to support approval should be designed with numbers large enough to detect a cardiovascular safety signal. The magnitude of that number was not specified by committee members”
What has DGIEP recommended since the AC?

• DGIEP has generally recommended that the safety development program for 5-HT4 agonists include initiation of a premarketing trial with adequate cardiovascular safety evaluation as its primary objective. This trial would not need to be completed prior to submission of the NDA.

• DGIEP anticipates that an AC would be held during the NDA review to determine whether the level of evidence submitted for cardiovascular safety is sufficient to allow approval of the drug product before completing the CV safety trial (or whether additional enrollment in such a trial may or may not be necessary).

• The Advisory Committee will consider among other things, the intended indication when weighing the risk benefit for a particular drug product.
Considerations:

- Potential safety signal arises from meta-analysis of clinical trial data
  - Unexpected result, small numbers, retrospective
  - Is it a signal?
- MOA
  - Platelet aggregation data and clinical interpretation
    - not an FDA approved test
    - Results and clinical meaningfulness in non-cardiac drugs
- Symptomatic Diseases, non-life threatening
- Post-market/pre-market considerations
  - Is it a class issue?
- Selective approval?
  - Events were seen in patients at risk for “CV” events
  - Does having one risk factor disqualify a patient from receiving a drug?
    - What about women under 30 who take BCPs? NSAIDS?
Possible platelet activation?


Investigations on 5-HT₄ receptor expression and effects of tegaserod on human platelet aggregation in vitro.

Serebruany VL, El Mouelhi M, Pfannkuche HJ, Rose K, Marro M, Angiolillo DJ.

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Abstract

• A meta-analysis of 29 clinical studies on tegaserod revealed an imbalance of cardiovascular ischemic events in patients treated with drug versus placebo. Because increased platelet activity is known to attribute to cardiovascular events, we examined the presence of serotonin receptor type 4 (5-HT₄) receptors and the effects of tegaserod on in vitro aggregation of human platelets. Blood samples were obtained from 20 healthy volunteers and 20 subjects with irritable bowel syndrome with constipation. Samples of whole blood-citrate mixtures were incubated with different tegaserod concentrations mimicking human Cmax values (10 nM), 3.3 times, and 10 times Cmax for at least 1 hour. Conventional plasma platelet aggregation was induced by adenosine diphosphate, collagen, thrombin receptor activating peptide, epinephrine, and serotonin plus adenosine diphosphate. Gene expression analyses targeting 5-HT₄ and serotonin receptor type 2 receptors were carried out using human platelet RNA. The presence of 5-HT₄ receptor protein was investigated by Western blot analysis using membrane fractions from human platelets. Preincubation with tegaserod resulted in mild but statistically significant increases in platelet aggregation induced by adenosine diphosphate, collagen, epinephrine, and serotonin plus adenosine diphosphate. The effects were comparable using thrombocytes obtained from healthy volunteers and patients with irritable bowel syndrome with constipation. Expression analysis revealed that mRNA encoding both 5-HT₄ and serotonin receptor type 2 receptors was present in human platelets. The expression of 5-HT₄ receptor mRNA was approximately eightfold lower than serotonin receptor type 2 receptor mRNA. Results from Western blot analyses examining the presence of 5-HT₄ receptor protein in human platelets were in agreement with the findings of the mRNA expression analysis. In platelets harvested from normal persons and patients with irritable bowel syndrome with constipation and exposed in vitro to tegaserod, we detected small but statistically significant concentration-dependent increases in induced platelet aggregation. The relationship of these in vitro effects to clinical cardiovascular ischemic events is presently unclear. Western blot analysis findings suggest the presence of 5-HT₄ receptor protein on human platelets. Further investigations on the potential role of 5-HT₄ receptors in human platelets may be warranted.
## Comments on Dr. Anderson’s Presentation

| Origin of potential CV safety signal | Retrospective database analysis | **Retrospective analysis of clinical trial data**  
Later studies presented by Dr. Anderson which contradict:  
**Retrospective analysis of health records database**  
**Retrospective analysis of health claims database** |
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<tr>
<td>Weight of Evidence</td>
<td>Weak</td>
<td>Potential effect</td>
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<tr>
<td>Presence of a Likely MOA</td>
<td>None identified</td>
<td>Platelet effect – clinical meaningfulness of the in vitro studies?</td>
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| BR Relationship                     | Appears high, especially in those without CV risk factors, indication for non-life-threatening condition | May be low given the availability of other drugs for the treatment of constipation  
However may be meaningful for patients who have failed other therapies and have significant impact on daily life |
| Is perceived risk:  
Generalizable to other drugs in class with same efficacy MOA? | doubtful | Do the pre-clinical data significantly influence considerations for conducting clinical studies? |
| Lessons Learned                     | Caution in subgroup interpretation where data are of poor quality, results unexpected, are not replicated in other databases, and occur in the absence of biological rationale | Agree regarding caution for all types of data  
What databases should be used in order to determine if this signal is not replicated?  
Is there a true absence of biological rationale? |