

DECLARATION OF ADAM SHEA

I, Adam Shea, declare:

1. I am a member in good standing with the California State Bar and am counsel for the Plaintiffs in this action. I have personal knowledge of the facts contained in this declaration, and, if called as a witness, I am competent to testify to those facts.

2. I make this declaration in support of Plaintiff’s Opposition to Defendants’ Motion for Summary Judgment.

3. Attached hereto as Exhibit 1 is a true and correct copy of an internal powerpoint presentation produced by Defendants.

4. Attached hereto as Exhibit 2 is a true and correct copy of a document entitled Takeda Pharmaceuticals Company, Ltd., Corporate Overview, dated March 24, 2008

5. Attached hereto as Exhibit 3 is a true and correct copy of a document entitled MAA EU Bladder Issue.

6. Attached hereto as Exhibit 4 is a true and correct copy of a correspondence file between Samuel Cohen and Takeda.

7. Attached hereto as Exhibit 5 is a true and correct excerpt of the Deposition of Samuel Cohen.

8. Attached hereto as Exhibit 6 is a true and correct copy of a document entitled Actos Submission Strategy 10 Mar 2004.

9. Attached hereto as Exhibit 7 is a true and correct copy of a document entitled FDA Conference Call August 13, 2002.

10. Attached hereto as Exhibit 8 is a true and correct copy of a facsimile from Antonio Cherchi to A Stuart on 24 July 2008.

11. Attached hereto as Exhibit 9 is a true and correct copy of deposition excerpts from

PANISH SHEA & BOYLE LLP
11111 Santa Monica Boulevard, Suite 700
Los Angeles, California 90025
310.477.1700 phone • 310.477.1699 fax

1 the deposition of David Brunsting.

2 12. Attached hereto as Exhibit 10 is a true and correct copy of a July 29, 2002 email
3 from Ingrid Hoos to David Baron et al.

4 13. Attached hereto as Exhibit 11 is a true and correct copy of a document entitled
5 Table 1.1 Disposition of Subjects.

6 14. Attached hereto as Exhibit 12 is a true and correct copy of a document entitled
7 Action plan for NN issue by DRSL.

8 15. Attached hereto as Exhibit 13 is a true and correct copy of a document produced by
9 Defendants summarizing discussions with the FDA.

10 16. Attached hereto as Exhibit 14 is a true and correct copy of FDA Meeting Minutes
11 dated February 4, 2003.

12 17. Attached hereto as Exhibit 15 is a true and correct copy of an April 8, 2011 email
13 from Jessie Lee to Eric Song.

14 18. Attached hereto as Exhibit 16 is a true and correct copy of a Contact Report Form
15 dated May 12, 2006.

16 19. Attached hereto as Exhibit 17 is a true and correct copy of an email from James
17 Lewis to Brian Strom on July 21, 2005.

18 20. Attached hereto as Exhibit 18 is a true and correct copy of a document titled
19 Pioglitazone and Neoplasia Expert Meeting.

20 21. Attached hereto as Exhibit 19 is a true and correct copy of a document entitled
21 Appendix D Kaiser Permanente Northern California Database

22 22. Attached hereto as Exhibit 20 is a true and correct copy of an email to Mick Roebel
23 dated August 8, 2005.

24 23. Attached hereto as Exhibit 21 is a true and correct copy of a June 19, 2006 contact
25
26
27
28

1 report.

2 24. Attached hereto as Exhibit 22 is a true and correct copy of an email to John Yates
3 dated June 6, 2006.

4 25. Attached hereto as Exhibit 23 is a true and correct copy of James Morrison's
5 Report.

6 26. Attached hereto as Exhibit 24 is a true and correct copy of a document entitled
7 Actos Family Momentum.

8 27. Attached hereto as Exhibit 25 is a true and correct copy of an email to Jennifer
9 Greeby dated September 17, 2010.

10 28. Attached hereto as Exhibit 26 is a true and correct copy of a document titled
11 Strengthen Your Core.

12 29. Attached hereto as Exhibit 27 is a true and correct copy of an email from Karen
13 Degen dated December 7, 2011.

14 30. Attached hereto as Exhibit 28 is a true and correct excerpt of plaintiff Jack
15 Cooper's November 8, 2012 deposition.

16 31. Attached hereto as Exhibit 29 is a true and correct excerpt of the deposition of
17 Darren McGuire, M.D., January 16, 2013.

18 32. Attached hereto as Exhibit 30 is a true and correct excerpt of the deposition of
19 Amanda Vaughn.

20 33. Attached hereto as Exhibit 31 is a true and correct excerpt of the deposition of
21 Kylie Wagner.

22 34. Attached hereto as Exhibit 32 is a true and correct copy excerpt of Report for Dr.
23 Greenberg.

24 35. Attached hereto as Exhibit 33 is a true and correct copy excerpt of correspondence
25
26
27
28

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

from Yasuchika Hasegawa;

36. Attached hereto as Exhibit 34 is a true and correct copy excerpt of correspondence relating to merger of Takeda;

37. Attached hereto as Exhibit 35 is a true and correct copy excerpt of document relating to the research and development activity of Takeda;

38. Attached hereto as Exhibit 36 is a true and correct copy of document identified as TAK-GREENS-00046781;

39. Attached hereto as Exhibit 37 is a true and correct copy of a document marked as TAK-RECKED_00146849;

40. Attached hereto as Exhibit 38 is a true and correct copy of a document marked as TAK-RECKED-00138184;

41. Attached hereto as Exhibit 39 is a true and correct copy of a document relating to the sales of Actos and marked TAK-RYANDA-00107858;

42. Attached hereto as Exhibit 40 is a true and correct copy email correspondence relating to Actos and identified as TAK-PERALM-00030005;

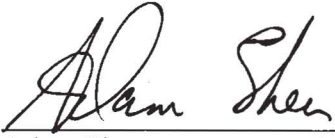
43. Attached hereto as Exhibit 41 is a true and correct copy of an EMEA request identified as TAK-BAROND-00129789;

44. Attached hereto as Exhibit 42 is a true and correct copy of a bladder cancer report identified as TAK-INDNDA-01177597’

45. Attached hereto as Exhibit 43 is a true and correct copy of a bladder cancer report identifiedas TAK-PHARMACO-0121312;

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

I hereby declare that the above statements are true and correct. Signed under the penalty of perjury under the laws of the State of California, on the date set forth below.



Adam Shea

PANISH SHEA & BOYLE LLP
11111 Santa Monica Boulevard, Suite 700
Los Angeles, California 90025
310.477.1700 phone • 310.477.1699 fax

EXHIBIT 1



Barriers to TZD Prescribing Qual Report

December 2003





Overview

| | <u>Slide #</u> |
|---|----------------|
| ■ BACKGROUND, OBJECTIVES, AND METHOD | 2 |
| ■ EXECUTIVE SUMMARY | 7 |
| ■ DETAILED FINDINGS | 21 |
| • Current Practices and Overall Attitudes | 22 |
| • Use and Perceptions of TZDs | 29 |
| • Other Factors Influencing Perceptions of TZDs | 42 |
| • Barriers to Prescribing TZDs | 49 |
| • Reactions to New Product Profile | 66 |
| ■ APPENDIX | 71 |

Background, Objectives, and Method





Background and Objective

- Despite growing evidence that TZDs offer unique, important long-term benefits as well as a proven safety record, many physicians limit their use of this class of oral antidiabetic medications (OADs).
- The objective of this research is to understand key factors that drive high-level prescribing of TZDs as well as identify barriers to use among low writers of TZDs.
 - Specific barriers addressed included:
 - Cost
 - Weight gain
 - Edema
 - Liver safety/liver function testing (LFT)
 - Cardiovascular safety



Method

- A total of 28 in-depth telephone interviews were conducted with endocrinologists and primary care physicians in November 2003.
 - Interviews were approximately 45 minutes in duration.
- The research was conducted in two phases
 - In the initial phase, in-depth telephone interviews were conducted with a total of 11 high TZD prescribers.
 - 4 Primary Care Physicians (PCPs)
 - 7 Endocrinologists (ENDOs)
 - In the second phase, in-depth telephone interviews were conducted with a total of 17 medium-to-low TZD prescribers.
 - 9 PCPs
 - 8 ENDOs



Note to the Reader: **High vs. Low TZD Prescribers**

This report presents the findings of low, medium, and high prescribers of TZDs, as defined by a Takeda list (See slide 73 in Appendix). Subsequently, the report is designed, in part, to elucidate the differences between high and low writers of TZDs.

Physicians identified as mid-level prescribers attitudinally had responses characteristic of either group.

Thus the attitudes of “high level” TZD prescribers as well as “low level” prescribers might include the responses from the medium-level group.



Caveat

This research is qualitative in nature and is based on a limited sample of primary care physicians and endocrinologists. This information is intended to provide direction to the ACTOS Brand Team but should not be considered projectable to the universe of each audience.

Numerical estimates (including estimates of patient volume, proportions of patients on TZDs, etc.) must be interpreted with special caution.



Executive Summary





Executive Summary:

Little change seen in treatment patterns

- The type 2 diabetes treatment paradigm has changed little in the past year.
 - With metformin the first-line OAD of choice, followed by add-on TZDs or sulfonylureas, as second line therapy.
 - Some physicians use TZDs as first line.
 - Starting with combination therapy of TZD plus metformin
 - These are typically high writers of TZDs; however, not all higher writers are first-line use advocates

- Treatment goals are also fairly consistent, focusing on hemoglobin A1c levels, lipid, and blood pressure control.
 - High prescribers of TZDs were somewhat more concerned with long-term complications of diabetes as well as endothelial cell function.



Executive Summary:

Characteristics of high vs. low TZD Rx'ers

- Principally, high writers differ from low writers in that they are:
 - More “sold” on the secondary target organ, lipid, and endothelial benefits of TZDs.
 - Willing to counsel patients on how the benefits outweigh the perceived drawbacks of TZDs.
 - Particularly higher costs/co-pays and weight gain.
 - Whereas low writers were more willing to quickly switch to another OAD class when patients complain about TZD drawbacks.
 - Apt to believe the mechanism of TZDs offers unique benefits in insulin resistance and Metabolic Syndrome.



Executive Summary:

Characteristics of high vs. low TZD Rx'ers

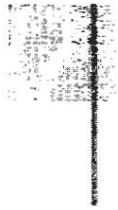
- High writing physicians of TZDs also tend to be:
 - Higher writers of metformin
 - However, they are not more likely to prescribe sulfonyureas
 - More likely to prescribe polypharmacy (related to above)
- Low writers often express that their main focus in OAD prescribing is managing blood glucose.
 - Several mentioned that other agents (e.g., statins, antihypertensives) can cover target organ protection better and more directly than TZDs.



Executive Summary:

Characteristics of high vs. low TZD Rx'ers

- Those physicians claiming to be more knowledgeable about secondary TZD benefits are more likely to be high TZD writers.
- However, low users claim that “there is nothing more that [they] could learn about TZDs that would change [their] prescribing.”
 - They prefer to rely instead on their own experience.



Executive Summary:
Overcoming Barriers

- Specific barriers are listed on the next pages.
 - They are in order of importance.
 - e.g., The first listed barrier is more of an issue than those that follow.



Executive Summary:
Overcoming Barriers

Barrier: Cost & Reimbursement

- Cost and reimbursement are the main barriers of TZD prescribing due to the availability of generic metformin.
 - Causing MCOs to mandate the use of metformin first line in many cases.
- Metformin is also seen as quite effective, demonstrating value.
- TZDs are higher priced and, therefore, have higher co-pays.

High writers overcome by...

- Telling patients that the value of target organ, cardiovascular and endothelial benefits of TZDs outweigh the higher cost.
- Considering the benefits of TZDs among insulin resistant patients.
- Using patient-assistance programs and samples.



Executive Summary: **Overcoming Barriers**

Barrier: Weight Gain

- Lower writers are more willing to discontinue TZDs when patients complain about weight gain.
 - A few avoid prescribing TZDs for patients they believe might be sensitive to the issue.

High writers overcome by...

- Turning the negative into a positive—the gain may be a result of improved glucose metabolism.
- Again, counseling the patients of the value of the secondary benefits of TZDs—overshadowing the weight gain.
- Not bringing up the subject of weight gain unless it manifests in a patient (and the patient complains).



Executive Summary:
Overcoming Barriers

Barrier: Edema

- While an important issue, few patients develop peripheral edema on TZDs or other OADs.
 - Some instances of TZD-related edema were transient.
 - TZDs are only rarely discontinued due to peripheral edema.
- There are no notable differences between the way high vs. low prescribers handle edema.

Physicians overcome by...

- Halving the TZD dose, if they believe the issue is dose-related.
- In a few cases, prescribing a diuretic.
- Confirming that the edema is not CHF related.



Executive Summary: **Overcoming Barriers**

Barrier: Liver Safety

- Liver complications is not a notable barrier among physicians in the study...
 - Except for a few patients with prior or active liver disease.
- MDs state liver function tests (LFTs) are not a barrier.

Physicians overcome by...

- Avoiding use among patients with a history of or existing liver disease.
- Realizing that most patients with type 2 require LFTs for other agents as well (e.g., statins).
- Personal experience: None of the physicians reported liver complications associated with ACTOS or Avandia use.



Executive Summary:
Overcoming Barriers

Barrier: CHF

- Congestive heart failure was not seen as a major barrier to writing TZDs.
 - Only a small minority of type 2 patients were reported to have CHF.

Physicians overcome by...

- Avoiding use among patients with CHF.
- Ruling out CHF if edema is present.
 - Testing for ejection fraction (mentioned by only a few respondents)



Executive Summary: **Overcoming Barriers**

Barrier: Onset of action

- A perceived slower onset was volunteered as a barrier to first-line use by about one-quarter of respondents.
 - Physicians concerned about this, particularly lower writers, opted to use other OADs first-line (among other rationale).

High writers...

- Typically were less concerned about slower onset; however most higher writers still used TZDs as second-line therapy.
- Sometimes initiate a patient on both a TZD and metformin, particularly if insulin resistant.



Executive Summary:
Recommendations

- Emphasizing to low writers on how to overcome these barriers will be an important step in increasing TZD use.
 - Particularly in weight gain
- Exposing low writers to data on the secondary benefits of TZDs will also be useful.
 - Such as increase target organ protection, lipid benefits, and endothelial benefits



Executive Summary:
Recommendations

- Educating low writers about the benefits of using *multiple* OADs earlier in the treatment sequence for patients with type 2—A metformin + TZD regimen could help with use earlier in the treatment algorithm.
 - High writers are often quicker to move to metformin + TZD polypharmacy than low writers.

Detailed Findings



Findings: Current Practices and Overall Attitudes



Current Prescribing Practices

- Prescribing practices of physicians varied, as shown below by percent of patients treating with each category of agent.
- High TZD prescribers wrote more prescriptions for both TZDs and metformin (but not sulfonylureas).
- High TZD prescribers were more likely to have greater numbers of patients on combination therapy than low/medium writers as seen in “total percentage” column below.

| | Metformin | Sulfonyl-ureas | TZDs | Other | Insulin | Total Percentage |
|-----------------------|-----------|----------------|------|-------|---------|------------------|
| High TZD Rx'ers | 63% | 35% | 52% | 11% | 24% | 185 |
| Low/Medium TZD Rx'ers | 54% | 37% | 32% | 10% | 29% | 162 |

N= 28 physicians: 11 high writers; 17 medium/low



Initial Therapy

- Both high and low prescribers of TZDs tend to start patients on metformin, because:
 - Metformin is seen as efficacious and is available in an inexpensive, generic form.
 - Many believe it is effective in the general diabetic population and among those with insulin resistance.
 - TZDs are more expensive, less available on formulary, and thus tend to be used later in the treatment sequence.
 - Metformin is seen as not increasing patient weight.



Efficacy Measures

- Not surprisingly, physicians focus on lab values to measure success of treatment, with an HbA_{1c} at 6.5 or below as a fairly consistent goal.
- Secondly, physicians look for efficacy in terms of impact on insulin resistance and among patients with Metabolic Syndrome, such as:
 - Lipid lowering
 - Prevention of long-term complications
 - Impact on blood pressure



Importance of Insulin Resistance

- Most physicians reported that the majority of their patients with type 2 have some degree of insulin resistance.
 - Most report 70% or more of their patients as insulin resistant.
 - There are no notable differences between high and low writers in terms of proportion of insulin resistant patients.



Importance of Insulin Resistance

- Perception of efficacy in insulin resistance reveals an important difference between high and low prescribers of TZDs.
 - High TZD prescribers more likely to believe that TZDs offer unique efficacy against insulin resistance.

“TZDs are first-line for insulin resistance, they treat the main pathophysiology of the disease.” High TZD Endo
 - Low TZD writers more likely to believe that metformin and TZDs are equally efficacious in treating insulin resistance.



Perceptions of Impact on Endothelium

- Most physicians were aware of some relationship between diabetic “control” and endothelial damage.
- High prescribers appear to have a better understanding of the importance of treating insulin resistance and preventing endothelial cell damage.

“It’s critically important to prevent inflammatory damage to endothelial cells. All the complications of diabetes are related to inflammatory cytokines.” High TZD PCP

“I don’t know about endothelial cell function. If the sugar can’t get into the cell, it’s resistant, it’s not utilizing sugar well.” Low TZD PCP

Findings: Use and Perceptions of TZDs





Order of Use of TZDs

- Regardless of level of use, most physicians in the study do not use TZDs as 1st line therapy.
 - Among higher TZD writers, about half in the study write TZDs, to any extent, as first-line therapy.
- Most commonly, TZDs are used as first or second *add-on*.
 - Typically added to metformin, although in some cases third to metformin and sulfonylureas.



TZD Candidate Populations

- Nearly all patients with type 2 diabetes are considered, by physicians, to be candidates for TZD therapy, due to:
 - Efficacy in lowering blood glucose.
 - Perceived cardiovascular and target organ benefits (particularly among high writers).
 - Mechanism of action, which helps patients make better use of their own insulin.



TZD Candidate Populations

- While the candidate population is large for TZDs...
 - Patients with Metabolic Syndrome are considered the *most likely* candidates for TZDs, particularly among high writers.
 - Thus, these are patients who tend to be:
 - Insulin resistant
 - Dyslipidemic
 - Obese
 - However, there is a perception that TZDs can increase patient weight to some extent.



TZD Candidate Populations

- Two main factors drove the higher use perceptions in Metabolic Syndrome:
 - A perceived greater efficacy for TZDs among high writers due to the mechanism of action.
 - The need for multiple OADs with this population (e.g., metformin + TZDs in combination).



TZD Candidate Populations

- Low prescribers tend to fall into two “camps”:
 - Those who do not perceive, or are uncertain about, any added value of TZDs over metformin.
 - The majority of lower writers in the study

vs.

- Those who see a broad range of benefits of TZDs, but find cost and/or formulary restrictions greatly limit their prescribing.



Inclusion/Exclusion of Candidates

- In general, however, low TZD writers were more likely to find reasons to *exclude* candidates for TZDs, such as:
 - Cost
 - CHF
 - Edema
 - Weight gain
 - Patients with current or prior hepatic abnormalities
 - Slower onset of action

“Can they be well controlled with cheaper drugs with less side effects?” Low TZD Endo



Inclusion/Exclusion of Candidates

- For many low writers, cost is the *primary* reason that prevents TZD candidates from being treated with a TZD.

“My patients are on fixed incomes, they have no Rx plan and are on Medicare. There is also a group in the middle that is not old enough to get Medicare.” Low TZD Endo

- Both high and low prescribers are more likely to cite tolerability or side effects as a reason for not treating candidates.

“The others were tried on TZDs and had fluid retention or were contraindicated by CHF or liver disease.” High TZD Endo

- In a few cases, patients refused treatment due to safety concerns or perceived risk of weight gain.
 - A few patients expressed concerns on TZDs after negative publicity about Rezulin according to two physicians.



Inclusion/Exclusion of Candidates

- On the other hand, high TZD writers are more likely to cite the benefits of TZDs, such as:
 - Treatment of insulin resistance
 - Improved lipid profile
 - Endothelial benefits
 - No risk of hypoglycemia



Inclusion/Exclusion of Candidates

- Those more apt to use TZDs first line—among high and medium-level writers—are also more likely to perceive unique benefits of TZDs, including:
 - Beta-cell preservation
 - Protection of endothelium
 - Slowing of disease progression



Focus on Primary vs. Secondary Benefits

- Among both high PCP writers and several ENDOs the perceived unique benefits of TZDs are important.

“It’s very important – the patient gets stable and you can expect a sustained response. Sustained response and insulin resistance are related. If you act on the cause...you treat the insulin resistance and protect the pancreas.” High TZD PCP

“TZDs treat the origin of the problem, helping the muscle to use insulin. It’s extremely important.” Low TZD Endo

- Others are less convinced of unique benefits, and are more focused on the “primary objective”—blood glucose control

“I understand the theory about long-term effects [with TZDs], but it’s not more efficacious [at reaching goal]. Reaching goal is key, it doesn’t matter which drug you use...local experts and ADA guidelines start with tight control with metformin, then sulfonylureas, then TZDs.” Low TZD PCP



Self-reported TZD Range of Usage

- High writers cite that, ultimately, about 50% – 75% of their patients with type 2 diabetes are prescribed TZD therapy.
- Lower writers self-report that 25% – 40% are prescribed a TZD regimen.



TZD Preference

- About two-thirds of physicians have no preference for ACTOS vs. Avandia.
 - The remaining physicians are evenly divided as to their preference, however, rationale is often related to the drug that is on formulary, availability of samples, and experience with the agent.

Findings:
Other Factors Influencing Perceptions of TZDs





High TZD Rx'ers More Knowledgeable

- Those more apt to write for TZDs are also more knowledgeable about secondary benefits of the class than their low-user counterparts.
 - Secondary benefits included lipid/cardiovascular benefits, target organ protection, use in insulin resistance, endothelial benefits.
 - In contrast, most low writers have only a passing knowledge of secondary claims and are more skeptical that any benefit would represent a meaningful improvement.
 - A few low writers, however, are more convinced of these claims, but found that the cost of TZDs outweigh the potential benefits.
- *However*, both high and low writers do not believe that there is anything more that they could learn about TZDs that would raise their level of use.



High TZD Rx'ers More Knowledgeable

- This creates a “disconnect” among physicians:
 - More knowledgeable respondents write more TZDs.
 - Less-informed physicians do not believe more TZD education could increase their writing.
- There are a few reasons given for this:
 - Some low writers prefer more personal experience with TZDs over (more) education.
 - For a few physicians, cardiac mortality data and other secondary benefits are still inconclusive.



Impact of Rezulin on TZD Perception

- Almost all physicians used Rezulin in the past.
 - Rezulin offered a novel mechanism of action and a means by which to add another oral agent rather than starting insulin.
 - Despite the later release of data showing liver toxicity concerns, many of the physicians reported excellent experiences with Rezulin.

“I used Rezulin because the literature was outstanding on efficacy. It was also a new class. My experience was very positive. It had no fluid retention.” High TZD Endo

“We used Rezulin for people with severe insulin resistance. It was more effective than the current TZDs.” Low TZD Endo



Impact of Rezulin on TZD Perception

- Following the release of liver toxicity data associated with Rezulin, physicians initially were concerned about safety of “newer” TZDs.
- However, nearly all physicians in the study had concerns about ACTOS and Avandia allayed over time due to:
 - Physicians’ own positive personal experience with the newer TZDs.
 - No evidence of TZD-caused liver toxicity among their patients.
 - Publications demonstrating safety and clinical benefits shown for ACTOS and Avandia.

“Initially when Rezulin was recalled, everyone was nervous. Over time, we have used TZDs more in combination...I’m happy with combination therapy. The side effect profile is OK. LFTs are not as critical. The combination of literature and experience and indications have opened up use. TZDs are safer than people think.” Low TZD PCP

“I have a good feeling about TZDs. It’s gotten more positive over time. They work well, so I use them.” Low TZD PCP



Description of TZDs to Colleagues

- When respondents were asked how they would describe TZDs to colleagues many said that they have some benefits and a good safety profile – regardless of their level of use.

“TZDs are very valuable, they have unique benefits and there’s a lack of understanding [among physicians] about their benefits and safety. Also, they don’t have time to educate patients if they are not familiar with the drugs, and it’s restricted by the HMO. It’s a shame that the patient doesn’t get the benefit.” Low TZD Endo



Description of TZDs to Colleagues

- Reluctance to use TZDs more widely by colleagues (and respondents themselves) is also attributed to:

- Inexperience
- Habit

“I’m just not in the habit of writing them (TZDs). I should use them earlier, studies show that they slow progression of disease and have benefits on lipids.” Low TZD PCP

- Lack of understanding of TZDs unique impact on insulin resistance.

“Primary care physicians do not know the endothelial benefits of TZDs, so they don’t push as hard. Cost is a big deal, but Medicare doesn’t stop me from trying to do what’s best for the patient.” High TZD Endo

Findings: Barriers to Prescribing TZDs





Barriers to Prescribing: Overall

- Among the barriers addressed in this research...
 - Cost and reimbursement are the most significant barrier to (increased) TZD prescribing.
 - Weight gain is perceived to be a moderate-level barrier.
 - Viewed as minor concerns, particularly relative to OADs as a whole, were:
 - Edema
 - Liver safety
 - Cardiovascular safety
 - Onset of action was volunteered (i.e., unaided) as a barrier to first-line use by about one-fourth of respondents



Barriers to Prescribing: Cost and Reimbursement

- Cost is seen as the greatest barrier to (increased) TZD use by most respondents.
 - Particularly low- and medium-level TZD prescribers
- TZDs are considered “expensive” relative to most commonly used OADs.
 - With metformin typically having a much lower co-pay and out-of-pocket cost.



Barriers to Prescribing: Cost and Reimbursement

- Cost is more often seen as barrier by low TZD prescribers.
 - These physicians are more likely to have patients that do not have prescription coverage.
 - Also, many patients with type 2 are on polypharmacy (statins, ACE inhibitors, antihypertensives, and so forth).
 - Coupons, samples and patient assistance programs are used widely by respondents.
 - However, patient assistance programs are claimed to be of limited value since many patients are not poor enough to qualify.
- High TZD writers are more likely to mention the use of samples as a way to offset the high cost.



Barriers to Prescribing: Cost

- Among the insured, high copays can also be a barrier, particularly when many patients with type 2 are taking multiple, expensive medications.
 - Low TZD prescribers are more likely to discontinue the TZD and switch to a cheaper class when patients complain of costs.
“About one third of patients refuse [a TZD] due to cost, or drop out due to cost – they will even request insulin.” Low TZD PCP
- High writers are more likely to counsel patients on TZD benefits in response to complaints about cost.
“When they complain about the cost, I tell them it’s a bargain, considering the benefits of preventing complications and long term cardiovascular disease.” High TZD PCP

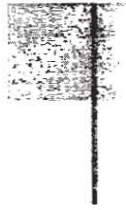


Barriers to Prescribing: Weight Gain

- Most physicians believe that minor weight gain is common among OADs, except for metformin.
 - Metformin is considered either weight-neutral or has the potential to help the patient lose weight.
 - Commonly reported weight gain with TZDs is in the range of 5 to 10 lbs., with a few higher exceptions.

- Generally, weight gain is seen as more of a patient tolerability issue rather than a medical issue.

“Weight gain is not an issue for the doctor, but all patients are very concerned. For the ones that follow their diet and exercise, it is not an issue.” High TZD Endo



Barriers to Prescribing: Weight Gain

- Some relate the weight gain to edema, while others attribute it to improved glucose metabolism.
- Several high writers turn reports of minor weight gain into a “positive” and evidence of the improved metabolism.
 - But stress the importance of returning back to their “normal” weight through diet and exercise.
 - Several stress to patients that taking OADs are not a “license to eat whatever they want.”



Barriers to Prescribing: Weight Gain

- For high writers, weight gain is not perceived as a major issue among most physicians prescribing TZDs.
 - However weight gain has the highest importance *relative to other barriers* for high writers.
 - Cost is relatively less important to this group of physicians.
- Low writers, who are less apt to consider secondary TZD benefits, are more willing to discontinue TZDs and/or switch to other OAD classes if a patient complains about weight gain.
 - A few doctors will avoid TZDs for patients they deem as more sensitive—in anticipation of weight gain complaints.



Barriers to Prescribing: Weight Gain

- Most high writers do not inform their patients about the potential for weight gain when prescribing, but prefer to address the issue if it arises.
 - When it does arise, high writers of TZDs are more likely to educate the patient about the unique, long-term benefits of TZDs—overshadowing the “risk of gaining a few pounds.”
- Nearly all physicians are interested in a predictive model as a tool to screen and counsel patients.



Barriers to Prescribing: Edema

- The incidence of edema is seen as lower than patients experiencing weight gain.
- Most respondents report about a 5% incidence of peripheral edema among their patients.
 - The edema was transient among some patients.
- Physicians do not see edema as a significant barrier in prescribing for TZDs or other OADs.
 - However, when edema occurs, physicians sometimes evaluate the patient to rule out the presence of CHF.



Barriers to Prescribing: Edema

- There are no significant differences between high and low TZD prescribers in terms of how they perceive and address edema.
 - Some consider edema to be dose-related and will lower the TZD dose.
 - Only a few are willing to prescribe a diuretic, which is perceived to be effective in about half the cases of edema.
 - Discontinuation of a TZD due to edema is generally rare.
- A predictive model for edema would be welcomed.



Barriers to Prescribing: Liver Safety

- The potential for liver toxicity does not appear to be a major barrier to increased use of TZDs.
- Physicians agree, regardless of TZD user status, that risk of liver dysfunction does not prevent them from using TZDs more widely.
 - Liver toxicity is considered to be very rare.
 - None of the physicians in the study have experienced a serious liver problem with a TZD patient.

"I have never had a problem with liver safety" High TZD PCP



Barriers to Prescribing: Liver Safety

- Nonetheless, physicians consider TZDs to be contraindicated for patients with prior or active liver disease.
 - Again, representing a minority of patients with type 2.
- Most do not consider periodic LFTs to be a serious inconvenience.
 - Many TZD patients are also on statins which require LFTs also.

“Liver monitoring is not a disadvantage, we’re doing it on everyone anyway.” High TZD Endo



Barriers to Prescribing: Cardiovascular Safety

- Most physicians do not see cardiovascular issues as a major barrier to TZD use.
- Nearly all agreed that TZDs are contraindicated for patients with NYHA classes III and IV CHF.
 - For most, this is a small number of patients.

“I do not have a problem with this, there are very few patients with CHF.” Lower user PCP
- A few physicians mentioned that they check ejection fraction when a patient is suspected of having CHF or is significantly at risk—prior to prescribing a TZD.



Barriers to Prescribing: Onset of Action

- Onset of action is also perceived as a barrier to first-line TZD use.
 - Volunteered by about one-fourth of physicians.

- These physicians prefer to use metformin or sulfonylureas to bring blood glucose levels down more rapidly.
 - Versus waiting 4 - 6 weeks to see an effect with a TZD.

Weighted Issues on Rx'ing decisions

- Physicians were asked to spread 100 points across five issues associated with TZDs: weight gain, edema, cost, liver safety and CV safety, in order to understand the extent to which each issue impacts TZD prescribing decisions .
- The table below shows the average points assigned to each issue.

| | Weight Gain | Edema | Cost | Liver Safety | CV Safety | TOTAL |
|-----------------------|-------------|-------|------|--------------|-----------|-------|
| High Rx'ers | 27 | 18 | 20 | 15 | 20 | 100 |
| Low/ Medium Rx'ers | 19 | 15 | 39 | 14 | 13 | 100 |



Weighted Issues on Rx'ing Decision

- As shown in the previous table, cost has a much greater impact on the prescribing decision for low prescribers of TZDs than on higher prescribers.
- As noted previously, high prescribers are more influenced by weight gain when considering prescribing a TZD.
 - The highest of the relatively low barriers for this population of physicians.



Findings: Reactions to New Product Profile





Reactions to New Product Profile

- In a limited number of interviews (n=12), physicians were presented with a profile of a new product and asked for their impressions and likelihood of use.
 - The results will help New Product Planning gauge an impact of hematuria monitoring for bladder tumors.



Reactions to New Product Profile

- The following profile was read to 12 physicians near the end of the interview:

I would like you to assume that there is a new class of oral antidiabetic agents that is similar to the TZDs or glitazones. I'd like to give you a very brief description of a potential product in this new class and get your reactions to it.

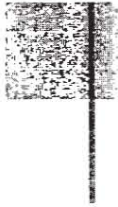
- Efficacy is comparable to TZDs as measured by A1c reduction
- The incidence of edema is less than TZDs
- The incidence of weight gain is the same as TZDs but the actual amount of weight gain is less.
- Periodic urinary monitoring is required to detect hematuria (blood in urine).
 - (Note to interviewer: If physicians asks, inform them that monitoring is recommended at baseline and then periodically thereafter, e.g. every 6 months)
- Assume all other aspects of this product are the same as the TZDs. (Note to interviewer: If asked, confirm liver monitoring is required as with the TZDs.)



Reactions to New Product Profile

- 8 of 12 physician initially expressed interest in using the new product.
 - While 4 physicians in 12 were concerned about the underlying problem causing hematuria.

“ I don’t like the hematuria part. What kind of problems would it cause with the kidneys?” Low TZD Endo
- Not surprisingly, those reacting positively did so due to the reduction in edema and weight gain incidence.
- Urine monitoring *per se* is not considered a barrier to use by the majority of physicians.
 - Most diabetic patients are having their urine monitored for albumin.
 - There is concern among some, however, as to potential safety issues that required the monitoring.



Reactions to New Product Profile

- Of the 8 physicians who expressed initial interest in using the product despite hematuria, interest declined when a risk of bladder tumors was introduced.

“Bladder tumors? That would change my thinking altogether. I would not be likely to use the product.” Low TZD PCP

- Interest declined greatly among 6 of the physicians.
 - Interest declined only slightly for 2 physicians.
- Of the 4 physicians initially concerned with hematuria, the risk of bladder tumors was serious enough that all felt they would not use the product.

“If there is a risk of bladder tumors, I would definitely not use it.”
Low TZD Endo

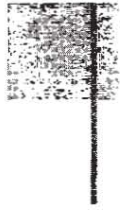


APPENDIX

Screening Criteria

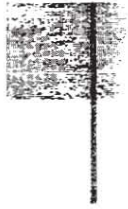
TZD User Definition





Screening Criteria

- Respondents were screened to meet the following requirements:
 - Less than 60 years of age
 - Devote greater than 75% of time to clinical practice
 - See the majority of their patients in an office based practice or clinic
 - Treat at least 15 patients with type 2 diabetes (ENDOs) and at least 25 patients with type 2 diabetes (PCPs) in a typical week
 - Write at least 1 prescription for OADs in a typical week
 - Standard security criteria



TZD User Definition

- High TZD User
 - 30% or more of OAD share is for TZDs

- Medium TZD User
 - 15% - 29% of OAD share is for TZDs

- Low TZD User
 - Less than 15% of OAD share is for TZDs