

## **DECLARATION OF SILVIO E. INZUCCHI, MD**

### **I. BACKGROUND AND QUALIFICATIONS**

1. My name is Silvio Inzucchi and I am presently Professor of Medicine at Yale University School of Medicine, in New Haven, Connecticut, where I also hold the positions of Clinical Director of the Section of Endocrinology and Program Director of the Endocrinology & Metabolism Fellowship. I am attending physician at Yale-New Haven Hospital, where I serve as Director of the Yale Diabetes Center.
2. I received my doctorate in medicine from Harvard Medical School, subsequent to which I undertook my internship and residency in internal medicine at Yale-New Haven Hospital. I later completed a postgraduate fellowship in Endocrinology and Metabolism at Yale University School of Medicine.
3. I am board certified in both the disciplines of Internal Medicine as well as Diabetes, Endocrinology and Metabolism. During my career, I have cared for more than 1,500 patients with diabetes. I have been elected as one of the *Best Doctors in America* for the past three years and was recently recognized as one of the Best Endocrinologists in the NY metropolitan area by *New York Magazine*.
4. I spend approximately 50% of my time in an academic clinical practice, where I have direct patient care responsibilities and also supervise postgraduate trainees. The remainder of my time is spent in teaching activities, administrative work, and conducting clinical research.
5. I have authored or co-authored over 200 articles, reviews, book chapters, and abstracts, some published in the worlds' leading scientific journals, including the *New England Journal of Medicine*, *JAMA*, the *Annals of Internal Medicine*, *Circulation*, and *Diabetes*

*Care*. I have recently edited the *Diabetes Mellitus Manual* (McGraw-Hill, 2005), which is an internationally distributed textbook for diabetes practitioners. I am the recent coauthor of the chapters on diabetes in one of the leading textbooks of internal medicine, *Cecil's Medicine*.

6. My research interests include the pharmacological management of type 2 diabetes mellitus ("Type 2 Diabetes"). I have collaborated on seminal research studies that have delineated the precise mechanisms of action of various oral agents for Type 2 Diabetes, with specific interest in the insulin sensitizers. More recently, my research has focused on the cardiovascular complications of diabetes and insulin resistance, namely coronary artery disease and stroke, and the management of the hospitalized diabetic patient.
7. I have served as a reviewer for medical journals, including the *New England Journal of Medicine*, *Lancet*, *JAMA*, *American Journal of Physiology*, *Diabetes Care*, *Diabetes*, and *Diabetic Medicine*, for whom I am typically asked to provide an expert opinion on the suitability of scientific manuscripts for publication, typically in the field of diabetes. I was recently the Associate Editor of the journal *Practical Diabetology* and currently serve on the editorial board of the newsletter *D.O.C. (Diabetes-Obesity-Cardiovascular Disease)* of the American Diabetes Association. I am a member of the American Diabetes Association, for whom I have taken part on several national committees, the European Association for the Study of Diabetes, and the Endocrine Society.
8. I have been an advisor to several pharmaceutical companies and investment houses to evaluate the efficacy, safety and future uses of anti-diabetic drugs. I am a frequently invited lecturer to professional audiences at major medical meetings both nationally and internationally. Over the past several years, I have presented at Columbia University,

New York University Medical Center, Albert Einstein College of Medicine, the University of Michigan, Case Western University, Tulane University, Wayne State University, and the University of Connecticut, as well as the annual scientific sessions of the American Diabetes Association and the American Heart Association, the national meeting of the Endocrine Society, and the annual congress of the International Diabetes Federation.

9. Having been a lecturer and researcher in this field over the past fifteen years, I have certain interests to disclose. I have given lectures for numerous pharmaceutical companies, including Takeda Pharmaceuticals North America, manufacturer of ACTOS® (pioglitazone hydrochloride), for which I have received honoraria. In addition, I have served on Advisory Boards for Takeda Chemical Industries, Ltd. (now Takeda Pharmaceutical Company Limited) and Takeda Pharmaceuticals North America, Inc. (collectively, "Takeda"). Takeda has also provided unrestricted educational grants to Yale University for Continuing Medical Education projects in which I have been involved, including printing of our diabetes informational booklets. I am also a co-investigator on the *Insulin Resistance Intervention after Stroke (IRIS)* study, an National Institutes of Health-funded clinical trial involving pioglitazone in stroke patients. Other than for technical regulatory matters, Takeda Pharmaceuticals North America has no input into the study's design, conduct, or interpretation of results. Takeda has not been involved in the funding of the primary study, although they have agreed to supply active drug and placebo.
10. I submit this declaration in support of a petition filed with the Food and Drug Administration by Takeda Pharmaceuticals North America that asks that generic versions

of pioglitazone not be approved with labeling that explains the use of the product only for monotherapy. In connection with this petition, I have the following opinions:

- Type 2 Diabetes is a complex, multi-system, and increasingly common metabolic disease, responsible for premature morbidity and mortality worldwide.
- The pathophysiological defects of Type 2 Diabetes involve both abnormal insulin action (i.e., “insulin resistance”) and inadequate insulin supply, both of which have genetic and environmental underpinnings. The metabolic end-result is a high blood glucose (sugar) level.
- High blood glucose has been linked to multiple complications, such as heart attacks, stroke, kidney failure, blindness and leg amputation – these sequelae account for the great majority of the financial and human costs of this disease.
- Reducing glucose levels will prevent or delay progression of the disease and its complications.
- The optimal treatment of Type 2 Diabetes includes lifestyle change, such as diet, weight loss and exercise, and in the vast majority of cases, pharmacological therapy with either oral or injectable medications.
- Type 2 Diabetes is a progressive disease with a predictable increase in blood glucose levels over time. As a result, pharmacological therapy with combinations of drugs is usually necessary to achieve adequate glucose control. Few patients, if any, will undergo drug therapy without utilizing a combination of drugs at some point in time.

- The thiazolidinedione (TZD) class of antidiabetic agents has been available since 1997 for clinical use in the United States. These insulin-sensitizing drugs have become increasingly popular to manage Type 2 Diabetes, notwithstanding the negative consequences caused by Rezulin, the first TZD approved and then removed from the market by the Food and Drug Administration.
- Today, ACTOS<sup>®</sup> (pioglitazone hydrochloride) is one of only two marketed TZDs. It is a unique compound with benefits demonstrated on not only glucose levels but also on other risk factors that predispose diabetic patients to early cardiovascular disease. Its uniqueness has been demonstrated in multiple comparative trials with other drugs both in and out of the TZD class.
- More widespread use of pioglitazone has been curtailed by concerns of weight gain and fluid retention. It is contraindicated in patients with advanced heart failure for this reason.
- Pioglitazone, like any TZD, is best used in combination with other antidiabetic drugs, especially metformin. This view is not only my own, but that of other thought leaders in the field. I estimate that the drug is used as first-line therapy (i.e., monotherapy) in less than 10% of cases. Moreover, in probably half of these situations, the drug is actually being used in an “off label” fashion – most likely for patients with “pre-diabetes” or those with “metabolic syndrome.” It should also be noted that those patients who are treated initially with pioglitazone as monotherapy will almost invariably require combination therapy with another antidiabetic agent at some point in time.

- It is predictable that generic pioglitazone, even if strictly labeled only for monotherapy use, will actually be prescribed mainly in combination with other antidiabetic agents. To suggest otherwise reflects either a naïve understanding of healthcare practices or a purposeful deception. Monotherapy with generic pioglitazone will most assuredly constitute a very small minority (much less than 10%) of these prescriptions, and these patients will almost always progress to combination therapy.
- My consulting fee is \$450 per hour. No part of my compensation is dependent upon the outcome of this matter.

11. The opinions I am expressing are entirely my own and are based on my education, training, and experience as described in my *curriculum vitae*, as well as on the published medical literature, including, but not limited to, the articles referenced herein.
12. Attached hereto is a true and accurate copy of my *curriculum vitae*, listing my academic appointments, invited lectures/presentations, honors, awards, and publications.

## **II. THE USE OF TZDS IN MONOTHERAPY AND IN COMBINATION WITH OTHER ANTIDIABETIC AGENTS**

13. Diabetes is a chronic metabolic condition characterized by elevated levels of blood sugar (glucose). It results from the insufficient supply or action of the hormone insulin. Insulin is a hormone that is made by specialized cells within the pancreas called the beta cells. Insulin essentially controls the blood glucose level (normal 70-100 mg/dl), driving glucose into the cells of the body where it is turned into energy. If the body is resistant to or has an inadequate supply of insulin, blood glucose levels rise. Diabetes is the result. Type 1 diabetes mellitus (“Type 1 Diabetes”) most frequently affects children and teens –

it results from the immune destruction of the beta cells. These patients make no insulin on their own and therefore need insulin injections to survive. Type 1 Diabetes comprises less than 10% of diabetes in this country and worldwide. Type 2 Diabetes is a more complex disease, involving dual defects – both insulin resistance *and* relative insulin deficiency. It remains controversial as to exactly which is primarily to blame, but most authorities agree that insulin resistance is the *fundamental defect* of Type 2 Diabetes, and, as such, can be found before the development of insulin deficiency. Notably, insulin resistance, by itself, does not lead to diabetes. However, when pancreatic secretion of insulin is insufficient to meet the insulin resistant individual's requirements, blood glucose levels climb, eventually into the diabetic range.

14. Diabetes affects more than 18 million Americans, with the vast majority having Type 2 Diabetes. Of these, one third are not yet aware that they have the disease and remain undiagnosed. Another 47 million Americans have glucose levels that are above normal, but not yet in the diabetic range (“pre-diabetes”). These individuals are at increased risk of developing diabetes, and the majority will likely do so over the next 5 years. During the past decade, the prevalence of diabetes has increased by more than 30%, especially in younger age groups and in certain ethnic groups, such as African Americans and Hispanic Americans. Diabetes affects 6% of the overall U.S. population. In certain age and ethnic groups, however, the prevalence approaches a staggering 25%. The recent increase in diabetes is linked to the increasing rates of obesity, which are ascribed to worsening dietary habits, more sedentary lifestyles, and the conveniences of the modern world. With more than 50% of adult Americans considered overweight and

approximately 20% actually obese, it is not surprising that diabetes is now considered an epidemic in the U.S.

15. Type 2 Diabetes develops from an initial period of insulin resistance and preserved, indeed augmented insulin secretion from the beta cells - as the pancreas tries to keep glucose levels normal by simply making more insulin. However, eventually, the beta cells become dysfunctional (some have used the term "exhaustion" which may or may not be an accurate description), and are no longer able to meet the body's demands for insulin. As a result, insulin levels fall and the blood glucose begins to rise. It is important to realize that in most patients with Type 2 Diabetes, other features coexist, including obesity, high blood pressure, and abnormal lipid (cholesterol) profiles. Each of these also increases the risk of cardiovascular disease. This constellation of abnormalities is often referred to as the "metabolic syndrome" or the "insulin resistance syndrome" (since some have proposed that the underlying defect is insulin resistance). It is now estimated that up to one-quarter of the U.S. adult population can be considered to have this syndrome. Accordingly, insulin resistance is a major area of scientific research. The discovery of the thiazolidinedione (TZD) class of medications (*see below*) revolutionized not only the treatment of Type 2 Diabetes, but also our understanding of the inter-relationships between insulin resistance, diabetes, and cardiovascular complications.
16. Due to the toxic effects of high glucose on blood vessels, patients with diabetes are predisposed to chronic complications involving disease within these vessels that feed critical organs. This results in kidney failure, blindness, leg ulcers and amputations, heart attacks and strokes. The predisposition to the latter two conditions, resulting from

blockages in large blood vessels (called "atherosclerosis"), is further heightened by the coexistence of those other risk factors (obesity, high blood pressure, and abnormal cholesterol). These complications encompass the major financial and human costs of this disease. Diabetic patients are 2-5 times more likely to suffer such a cardiovascular event than non-diabetic patients.

17. Type 2 Diabetes may be treated with lifestyle changes (i.e., diet, weight loss, and exercise), which forms the foundation of any therapeutic program. Unfortunately, these steps are usually insufficient to reduce blood glucose to a range that is considered healthy by the American Diabetes Association (90-130 mg/dl before meals). Accordingly, the vast majority of patients with Type 2 Diabetes will require at least one, and usually more than one, oral medication. A substantial proportion of patients will actually ultimately need insulin injections, similar to patients with Type 1 Diabetes. (Note that the insulin resistance in Type 2 Diabetes is not complete – that is, insulin will still lower blood glucose in these patients if given at the right dosage). Most physicians begin with any one of a number of oral agents as first-line therapy in the patient who is not controlled by diet and exercise alone. Subsequently, oral agents with different mechanisms of action are then combined. There is an increasing trend to begin with combination therapy, as the glucose level will be reduced more quickly and ultimately more substantively than with a single drug. As the disease progresses, insulin is either added to oral agents or replaces them entirely. The United Kingdom Prospective Diabetes Study (UKPDS) clearly demonstrated that diabetes is a progressive disease, with the seeming inexorable failure of beta cells as time passes. Accordingly, combination therapy is the rule in diabetes, not the exception.

18. The recommended pharmacological approach to Type 2 Diabetes has changed markedly over the past decade, with now nine distinct drug classes available on the U.S. market, each of which lower glucose via a different mechanism and each has unique advantages and disadvantages. Six of these are oral agents. The three major classes (sulfonylureas, metformin and thiazolidinediones) reduce glucose to a comparable degree. There is no ideal drug or combination of drugs for all patients. The optimal clinical approach is predicated on the experienced physician understanding the characteristics of each agent, how it works, and what side effects to expect. Tailoring the best program for each patient is, admittedly, sometimes more art than science.
19. The *sulfonylureas*, the oldest drug class for Type 2 Diabetes, stimulate more insulin production by the pancreas. They lead to weight gain and sometimes drop blood glucose too low. Such "hypoglycemia" can be life threatening and is a feared complication of this class. Some have suggested that sulfonylureas might also increase cardiovascular risk - a claim that is not well substantiated in the literature.
20. The *meglitinides* work very much like the sulfonylureas. They differ insofar as their onset and duration of action are much more rapid - they therefore need to be taken several times per day, just before meals. One advantage with the meglitinides is that they lower blood glucose levels right after meals better than sulfonylureas. They also likely have less risk of hypoglycemia and weight gain.
21. The *alpha-glucosidase inhibitors* interfere with the absorption of starches in the intestine, thereby retarding the usual increase in blood glucose levels following a meal. These drugs are not very popular in the U.S. because they are less effective than other classes and also frequently lead to intestinal gas and abdominal distress.

22. *Metformin* is a “biguanide” medication, and, unlike sulfonylureas and meglitinides, does not stimulate insulin production. Metformin instead reduces the liver’s production of glucose. The main benefit of metformin is that it does not lead to hypoglycemia. It also commonly results in some weight loss (or at least no weight gain). Metformin was also shown in the UKPDS to reduce the risk of heart attack and stroke in overweight patients with Type 2 Diabetes – the only drug to do so in any such study to date. As a result, most authorities consider it the best first choice for treating Type 2 Diabetes in the newly diagnosed patient. It remains and likely will continue to remain the most popular antidiabetic drug in the world. Disadvantages of metformin include diarrhea, which is usually mild and resolves with continued use, and lactic acidosis, a rare but severe side effect, typically seen when the drug is mistakenly given to patients with kidney failure.
23. The *dipeptidyl peptidase-IV (DPP-IV) inhibitors* are newer drugs that inhibit the degradation of gut-derived hormones known as incretins (GLP-1 and GIP). Incretins stimulate insulin release in response to meals. Additionally, they decrease the secretion of glucagons, another pancreatic hormone that serves to increase glucose levels. Incretins also slow the emptying of the stomach contents into the small intestine. By inhibiting the enzyme that metabolizes incretins, both GLP-1 and GIP concentrations are increased. Thereby, the DPP-IV inhibitors serve to lower glucose levels.
24. Finally, *thiazolidinediones (TZDs)* (e.g., rosiglitazone, pioglitazone) lower glucose by reducing insulin resistance (“insulin sensitizers”), primarily in fat and muscle, but also to some degree in the liver. This effect occurs through the binding of the drug to a receptor inside the nucleus of the cell, known as “PPAR-gamma”. Binding to PPAR-gamma results in its activation, and, subsequently, the production of a variety of proteins by the

cell that affect glucose metabolism. The net result is to allow, under the direction of insulin, more glucose inside the cell and out of the blood stream. So, TZDs improve a cell's sensitivity to insulin. While the TZDs share many metabolic effects, some are unique to the specific drug, likely due to an intricate molecular relationship between PPAR-gamma and the TZD compound. Pioglitazone, for instance, has been recently shown to exert benefit on a number of aspects of metabolism - specifically cholesterol levels - that are likely the result of its specific molecular composition. In addition, pioglitazone was recently demonstrated to reduce adverse cardiovascular events in high-risk patients with type 2 diabetes. Notably, the other TZD, rosiglitazone, was recently suggested to have the exact opposite effect - to increase cardiovascular events. This difference between two members of this class of medication underscores the unique character of each. It is therefore difficult to consider these agents within a group - each must be evaluated for its own merits (and risks). The glucose-lowering effects of TZDs are similar to those of other anti-diabetic medications.

25. Advantages of the TZDs include lack of hypoglycemia, as well as beneficial effects on certain risk factors for cardiovascular disease (e.g., insulin levels, distribution of body weight, blood pressure, cholesterol levels, tendency to blood clot formation, blood vessel inflammation, and various indirect markers of atherosclerosis.) These effects have mainly been demonstrated in small studies, mainly in animal models, but also to some degree in humans. Recently, pioglitazone was confirmed to improve cardiovascular outcomes in the PROactive study (Dormandy *et al.*, Lancet 2005.) Other benefits of TZDs include a slowing of the decline in beta cell function, which results in more durable effectiveness on glucose lowering, as compared to other therapies.

26. An earlier TZD, troglitazone (Rezulin), was associated with rare but often severe toxicity to the liver. Accordingly the drug was removed from the market in 2000. Thankfully, no such association has been reliably described with pioglitazone (ACTOS®). Nonetheless, some doctors remain reluctant to prescribe TZDs because of the history of this class. More concerning side effects of the current TZDs are weight gain and fluid retention, the latter leading to swollen ankles, particularly when the drugs are used at higher doses or in combination with insulin. Because of the fluid retention, they should not to be used in patients with advanced heart failure, which occurs frequently in Type 2 Diabetes patients. Another disadvantage of the TZDs is their slow onset of action – often taking weeks or even months to achieve their ultimate effect on glucose.
27. Even when used in monotherapy, progression to treatment involving combination therapy with other agents will virtually always occur. One authoritative consensus statement by the American Diabetes Association and the European Association for the Study of Diabetes recommended that the TZDs be used mainly as add-on drugs to patients not achieving adequate control with metformin (Nathan *et al.*, Diabetes Care 2006.)
28. Because the oral agents target different metabolic defects of Type 2 Diabetes, they are often used together to exert added benefit on glucose levels. Since Type 2 Diabetes is a progressive disease, combination therapy is indeed the only way to maintain good glycemic control over the long term in most patients. Generally, the addition of one drug class to another results in a greater glucose level reduction than would have been expected by using a single agent by itself. Most combinations are approved by the Food and Drug Administration, except for a sulfonylurea and a meglitinide. Single agents consisting of two drugs in fixed combinations, (i.e., metformin + sulfonylurea, metformin

+ TZD) are now also available. Several studies have also demonstrated the effectiveness of “triple therapy”, i.e., metformin + sulfonylurea + TZD.

29. Even after metformin was approved in the U.S. in 1995 for treatment of diabetes, the beneficial effects of combining a TZD with metformin were not known for quite some time. In 1997, I was involved in a clinical trial to test a hypothesis concerning whether troglitazone and metformin could be used in conjunction, with an additive effect. That was not something that was known before our study. One could have as easily proposed that, because both drugs are insulin sensitizers, their combined use would have no benefit. Clinical trials such as this one are conducted in order to determine whether a hypothesis is correct, and often result in a hypothesis being proven wrong. With metformin and troglitazone, the mechanisms of action were suspected to be somewhat different by experts in the field, but they both were felt to sensitize the body to insulin, so it was conjecture at the point we conducted our clinical trial whether or not the study would be a positive or negative study. It ended up being a positive study. I believe that it was an important study, because it led to studies being conducted that eventually led to the indication for that combination. More importantly, it underscored the importance of combination therapy to achieve glucose control in patients with Type 2 diabetes. Sometime after the clinical trial, we began to prescribe those two drugs in combination.
30. There is reasonable agreement that the ideal first-line drug for the typical Type 2 Diabetes patient not achieving good glucose control with lifestyle changes alone is metformin. I, as well as some of the most respected authorities in the field, have endorsed such an approach. The aforementioned recent consensus statement also endorses this approach (Nathan *et al.*, Diabetes Care 2006.) Previously, sulfonylureas

were the mainstay of therapy. Since the availability of metformin, however, it has become the most widely prescribed agent. While the TZDs hold promise, they remain most frequently used in combination with either metformin or sulfonylureas. They are also used in combination with insulin. There are several explanations for these trends. First is the TZDs' side effect profile – weight gain and fluid retention remain problematic. (Interestingly, there is some evidence that weight gain can be mitigated when the drug is used in combination with metformin). TZDs also have a delayed onset of action, and their maximal effect is exerted weeks after that of other drug classes. Also, the drug class works well in combination with others, with some studies even suggesting a synergistic effect. Given the progressive nature of Type 2 Diabetes and the limited effectiveness of any one agent, whatever drug is started initially, the addition of a second agent is likely to be required a short time thereafter, likely within the first years of therapy for most patients. Some authorities now endorse the notion of rapid progression (i.e., within several months) to additional agents if inadequate control is achieved with one drug, or even, as mentioned above, initiating two drugs at one time. These trends will likely continue. In fact, with increasing availability of cost-effective single drug products that combine two different pharmacological agents, early use of combination therapy is becoming increasingly popular and may some day become the standard approach to managing type 2 diabetes.

31. My preferred combination of drugs for treating patients with type 2 diabetes is a metformin with a TZD or a DPP-IV inhibitor. I believe that most diabetic patients should be on metformin first as first-line therapy and then treated with a combination of metformin and a glitazone, preferably pioglitazone, or sitagliptin (a DPP-IV inhibitor)

32. In my large diabetes practice, I estimate that less than 5% of patients are using TZDs alone to treat their diabetes. In all other cases, the drug is being used in combination with metformin and/or sulfonylureas and/or insulin. The small minority of patients for whom I prescribe Actos® as monotherapy generally are patients who cannot take metformin. (And as I have stated previously, I would expect these patients to transition to combination therapy at a later point in time.) The most popular combination in my practice is metformin + TZD (I would estimate that more than 75% of my patients on a TZD are also taking metformin). Our group actually published the very first experience with this specific combination - to target insulin resistance in *both* liver and muscle - and we have been strong proponents of this amalgam for years. Recently, one TZD (rosiglitazone) has been combined with metformin in a single tablet, and, I understand that pioglitazone will soon be available in a similar combination pill. Such availability will further increase the implementation of combination therapy.
33. I understand that some have based an assessment of the percentage use of TZDs in monotherapy on national data compilations, such as pharmacy-driven databases. I question the reliability of such data. National sales figures with respect to percentages of TZD prescriptions being used for monotherapy are difficult to interpret. Those difficulties arise because the data compilers never know what the patients are taking, if they are taking medications prescribed by more than one physician, if they are getting prescriptions filled at more than one pharmacy, if they are getting refills at a predicted rate, or if they are getting samples, so it is very difficult to understand exactly what is going on in the marketplace from marketing data. Such data compilations, such as

pharmacy-driven databases, provide data that is somewhat suspect, because you cannot track a specific prescription to an individual person because of privacy rules.

34. In my community, the TZDs are used as monotherapy at a given point in time in no more than 10-15% of cases, and virtually all of these cases will progress to combination therapy at some later point in time as their disease progresses. I'd further estimate that in half of monotherapy patients, the drug is actually being used in an "off label" fashion – i.e., in patients with pre-diabetes or with metabolic syndrome. Therefore, the use of a TZD as first-line therapy in Type 2 Diabetes constitutes a very small minority of patients. These trends are likely not unique to Connecticut, although I am not aware of the precise breakdown of TZD by patient use throughout the U.S. Based on my personal experience, conversations with colleagues, primary care physicians and my own practice, however, I believe that the national average of Actos<sup>®</sup> prescriptions that are being used for monotherapy of diabetes is less than 10% overall. The basis for my assessment of the percentage use of the prescriptions of Actos<sup>®</sup> for monotherapy is based on my experiences as an endocrinologist and as a lecturer to tens of thousands of primary care physicians and subsequent discussions. I would also doubt that the relative use of this drug class, in respect to others, is likely to change appreciably for the foreseeable future. In my assessment, the use of Actos<sup>®</sup> in monotherapy is an insubstantial use of the drug, and is transitory for virtually all patients. My understanding of the word "insubstantial" is that it means relatively minor compared to other uses of the drug. I believe that that will be the case for the foreseeable future.
35. In further support of combined metformin-TZD use, our group has recently investigated the benefit of these insulin sensitizers in older patients with Type 2 Diabetes who had

been discharged from the hospital with either heart failure or a heart attack. We found that the combination of metformin + TZD appeared to exert the greatest benefit, with death rates reduced by almost 50% in one study. Accordingly, I feel that, barring any active contraindications to metformin use, a TZD should essentially always be prescribed upon a foundation of metformin therapy.

36. In September of 2005 the results of the PROactive study (Dormandy *et al.*, Lancet 2005.) were announced. PROactive is the first study to examine the effects of TZDs on cardiovascular endpoints in patients with Type 2 Diabetes. Conducted in Europe, the trial's design was to compare the clinical outcomes in Type 2 Diabetes patients with stable coronary artery disease following the addition of pioglitazone vs. placebo to established antidiabetic therapy, mainly with sulfonylureas, metformin and/or insulin. While the results of the PROactive study with respect to the effects of TZDs on cardiovascular disease were less than expected in that they show that Actos<sup>®</sup> has a relatively mild effect on cardiovascular events, the study does show that Actos<sup>®</sup> improves cardiovascular outcome in patients with type 2 diabetes who are at high cardiovascular risk. The results do not change the position of the Actos<sup>®</sup> in terms of when and under which circumstances it should be used. Now that the PROactive study has come out, I remain cautiously optimistic concerning the potential beneficial effects of pioglitazone with respect to cardiovascular events, but the results of that study were not strong enough to change my prescription strategies to date. The conclusion that can be drawn from this trial is that the *addition* of pioglitazone to other therapies in Type 2 Diabetes reduces cardiovascular risk. Accordingly, if anything, it stands to reason that the use of pioglitazone in combination with other drugs will increase even further. If anything,

however, prescriptions of pioglitazone for monotherapy use has decreased since publication of the results of the PROactive study.

37. Generic drugs are used by physicians in the exact same fashion as the original branded product. Therefore, even when a generic drug is introduced into the U.S. market, practicing physicians will always continue to prescribe the drug (branded or generic) in the same way that they prescribed the branded product before the generic formulation became available, irrespective of what information is provided in the package insert for the generic drug. It is therefore utterly unreasonable to expect that physicians will be able to distinguish generic from brand name drugs as regards to specific use indications. Indeed, these decisions are usually made by dispensing pharmacists and health insurance policy makers, who are also unlikely to follow specific package insert guidelines, to maximize their cost savings. Therefore, in my estimation, the release of generic pioglitazone into the U.S. marketplace will immediately, automatically and overwhelmingly result in substitution of generic pioglitazone for ACTOS® in combination with metformin, sulfonylureas, DPP-IV inhibitors and/or injectable products such as exenatide and/or insulin formulations.
38. For purposes of illustration, let us assume that my community estimates for pioglitazone prescriptive frequency above (paragraphs 32-34) are correct and apply generally throughout the U.S. Accordingly, for each appropriate prescription for generic pioglitazone as monotherapy, there will be more than 10 inappropriate prescriptions for generic pioglitazone in combination therapy. Thus, more than 90% of generic pioglitazone prescriptions will be for uses involving the combination of generic pioglitazone with metformin, sulfonylureas, and/or insulin.

I declare under penalty of perjury that the foregoing is true and correct. Executed on July 28, 2007.

  
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Silvio E. Inzucchi, M.D.